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Precision Medicine and its Application to Chemical and Biological Diagnostics

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Executive Summary

Developments in biotechnology domains such as genetics, pharmacology, biomarker identification, and medicine reveal an increased focus on treatment strategies that are based on, and act upon, an individual's unique biological characteristics. Theoretically, all clinical decisions should be "personalized" in order to enable better outcomes for individual patients, but advances in the biosciences have only recently begun to develop precise approaches.

With omics[1] data, such as genomics, becoming more readily available, we now have a greater understanding of population-scale variation. The implementation of precision medicine concepts can help translate medical and biological data into actionable clinical decisions. Precision medicine is defined as the "tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment."[2]

Given the specificity and adaptability of precision medicine concepts, it is reasonable to think that these concepts could help bring clarity to the field of chemical and biological (CB) diagnosis and treatment in the military. The increasing amount of omics data could allow for enhancements to employed diagnostic systems and medical countermeasures for CB agents to improve clinical outcomes in the future. The Defense Threat Reduction Agency (DTRA) Research and Development (R&D) Directorate has been tasked with maintaining the U.S. military's technological superiority in countering weapons of mass destruction (WMD) and emerging threats. In turn, the directorate's Detection and Diagnostics Division tasked the Institute for Defense Analyses (IDA) to analyze how precision medicine technologies and concepts could be integrated with future chemical and biological diagnostics systems.

The IDA team performed a literature review to identify recent advancements made in precision medicine related to chemical and biological diagnostics. The literature review identified a number of studies outlining various precision medicine concepts and technologies, including omics analytical techniques, the applicability of precision medicine to biological and chemical agents, and state-of-the-art technologies. The research team also identified representative companies and products currently on the market to gauge the state of precision medicine.

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1 In this paper, the term "omics" refers to a broad panoply of technologies, including domains such as genomics, proteomics, and metabolomics.

2 President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* (Washington, DC: Executive Office of the President, September 2008), https://scholarship.rice.edu/bitstream/handle/1911/113024/pcast0036.pdf?sequence=1.

We found that the majority of clinical implementations of precision medicine concepts are focused on non-communicable diseases, including a great deal of cancer research; there is a lack of research directly tying precision medicine, diagnostics, and CB agents. We also observed that the implementation of precision medicine concepts in diagnostic technologies would not necessarily lead to better diagnoses, but would improve the characterization of patients, leading to improved clinical outcomes based on more personalized treatment.

Precision medicine concepts primarily implement patient data to guide clinical decisions. Because diagnoses are less dependent on individual patient characteristics, precision medicine concepts do not necessarily improve diagnoses or detection in the traditional sense, as they are not designed to yield increases in sensitivity or specificity.

We recommend using the information from this analysis to identify precision medicine concepts that could complement CB diagnostic technologies and make the leap from a traditional one-size-fits-all approach to medicine. The technologies highlighted in this study span multiple focus areas, but currently precision medicine concepts could apply to various scenarios such as patient monitoring in Role 3 facilities, or genetically profiling individuals in order to both characterize their susceptibility to chemical or biological agents and predict their responses to therapeutics.

The information in this research highlights the need to acquire technologies and create large datasets representing the appropriate populations to pursue precision medicine; this supporting data could be used to engage with DoD research program managers focused on the development of tailored therapeutics, patient monitoring at medical treatment facilities, and pre-deployment risk screening. We have highlighted the need to develop precision medicine datasets and technologies relevant to chemical and biological agents for the pursuit of precision medicine. The domains of diagnostic technologies, precision medicine, and omics fields are fast-moving with advances occurring rapidly, and constant monitoring is needed to capture opportunities which may not have been obvious before.

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1. Introduction

The term "precision medicine" first rose to prominence in a U.S. National Research Council publication that aimed to inspire a taxonomy database for disease classification. Precision medicine is defined as "the tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment."[3] The publication states that "precision medicine" conveys the goal that subgroups of patients could be defined and targeted in more specific ways; though similar, the term "personalized medicine" can inadvertently imply that therapeutics are developed for individuals and does not convey the tie between broad-scope research and patient characteristics as well as "precision medicine."

Since the completion of the first human genome sequence in 2003, clinicians have anticipated this data-driven transformation in healthcare. The current state of healthcare is changing, from a one-size-fits-all approach to a "P4" approach, or one that is predictive, preventive, personalized, and participatory.[4] Precision medicine fits into this approach by outlining how patient information, such as genetic data and clinical profiles, can result in different phenotypes to improve clinical outcomes. The authors of the National Research Council's publication may have focused on heterogeneity of treatment effect (i.e., the varying efficacy of treatment and potential adverse effects among subpopulations of patients),[5] but precision medicine can include all aspects of medicine which lead to better outcomes, including identifying high-risk patients for earlier or more aggressive interventions.

This analysis provides an overview of the current state of precision medicine and potential future implementations, with a focus on chemical and biological (CB) diagnostic technologies. The field of precision medicine is broad and rapidly changing, and this analysis highlights representative technologies and concepts in various subdomains of precision medicine, in order to help decision-makers determine what may be most useful in a given situation.

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3 National Academies Press, *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* (Washington, DC: National Academies Press, 2011), https://www.ncbi.nlm.nih.gov/books/NBK91503/.

4 Qi Wang et al., "Toward Multiomics-Based Next-Generation Diagnostics for Precision Medicine," *Personalized Medicine* 16, no. 2 (2019), https://doi.org/10.2217/pme-2018-0085.

5 David M. Kent et al., "Assessing and Reporting Heterogeneity in Treatment Effects in Clinical Trials: A Proposal," *Trials* 11, no. 1 (2010), https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-11-85.

Chapter 2 outlines the scope and methodology of the analysis. Chapter 3 outlines a variety of precision medicine technologies and highlights their relevance to chemical and biological diagnostics, when possible. Chapter 4 provides a non-exhaustive market analysis that highlights a few representative commercially available products and commercial entities that are prominent in the precision medicine field. Chapter 5 outlines the future of precision medicine, with some observations and suggestions for next steps for its complement within CB diagnostics.

2. Methodology

The analysis presented here is primarily a literature review of current precision medicine technology and concepts, applicable to CB diagnostic technologies. To scope out the sub-domains of interest, we performed an initial survey of literature to establish a definition of "precision medicine," identify the differences between precision medicine and other terms such as "personalized medicine," and create an overview of the current state of precision medicine.

We implemented three approaches when performing the literature review and our analysis:

- **A diagnostic target-based approach:** This approach included searches for different forms of data which could be used as inputs for precision medicine implementations of diagnostic technologies.
- **A technologies-based approach:** This approach highlights various novel diagnostic technologies which are relevant to precision medicine. A plethora of novel technologies have been developed in this domain, and many of these technologies have been captured in another recent IDA analysis, which may act as an extension to this approach.[6]
- **An agent/disease-based approach:** This approach attempts to highlight the potential for precision medicine to be applied to various chemical and biological agents, identifying avenues for diagnostic technology implementations.

A. Considerations

1. Precision Medicine

As defined by the President's Council of Advisors on Science and Technology (PCAST), precision medicine (PM) is the "tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."[7] The term "precision medicine" has been defined similarly by multiple institutions, but the use of the term in this study refers to the PCAST definition.

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[6] Catherine Scheible et al., Analysis of State-of-the-Art Diagnostics for Far-Forward Use, IDA Paper P-33049, (Alexandria, VA: Institute for Defense Analyses, July 2022).

[7] President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine.*

Personalized medicine differs from precision medicine in that personalized medicine refers to an approach to patients which considers their genetics, but also includes their preferences, beliefs, attitudes, knowledge, and social context.[8] Precision medicine relies heavily on data, analytics, and information, and generally does not include physician input. Table 1 highlights several examples of precision medicine concepts in genomics. The table only highlights genetic examples, but precision medicine is not limited to genetics and includes multiple other domains, including additional omics-based technologies, which are expanded upon in later sections of this analysis. The overall aim of precision medicine as a concept is to improve patient outcomes by allowing clinical decisions based on stratified patient data.

Table 1. Examples of Precision Medicine

Condition	Gene	Action
	Mendelian Disease[A]	
Cystic fibrosis	*CFTR*	Specific therapies such as ivacaftor and a combination of lumacaftor and ivacaftor
Long QT syndrome	*KCNQ1*, *KCNH2,* and *SCN5A*	Specific therapy for patients with *SCN5A* mutations
Duchenne muscular dystrophy	*DMD*	Ongoing phase III clinical trials of exon-skipping therapies
Malignant hyperthermia susceptibility	*RYR1*	Avoid volatile anesthetic agents; avoid extremes of heat
Familial hypercholesterolemia (FH)	*PCSK9*, *APOB,* and *LDLR*	• Heterozygous FH (HeFH): eligible for PCSK9 inhibitor drugs • Homozygous FH (HoFH): eligible for PCSK9 inhibitor drugs in addition to lomitapide and mipomersen
Dopa-responsive dystonia	*SPR*	Therapy with dopamine precursor L-dopa and the serotonin precursor 5-hydroxytryptophan
Thoracic aortic aneurysm	*SMAD, ACTA2*, *TGFBR1*, *TGFBR2,* and *FBN1*	Customization of surgical thresholds based on patient genotype
Left ventricular hypertrophy	*MYH7*, *MYBPC3*, *GLA,* and *TTR*	Sarcomeric cardiomyopathy, Fabry disease and transthyretin cardiac amyloid disease have specific therapies

[8] Geoffrey S. Ginsburg and Kathryn A. Phillips, "Precision Medicine: From Science to Value," *Health Affairs (Project Hope)* 37, no. 5 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5989714/.

Precision Oncology[B]		
Lung adenocarcinoma	*EGFR* and *ALK*	Targeted kinase inhibitors, such as gefitinib and crizotinib
Breast cancer	*HER2*	HER2 (also known as ERBB2)-targeted treatment, such as trastuzumab and pertuzumab
Gastrointestinal stromal tumor	*KIT*	Targeted KIT kinase activity inhibitors, such as imatinib
Melanoma	*BRAF*	BRAF inhibitors, such as vemurafenib and dabrafenib
Pharmacogenomics[C]		
Warfarin sensitivity	*CYP2C9* and *VKORC1*	Adjust dosage of warfarin or consider alternative anticoagulant
Clopidogrel sensitivity, post-stent procedure	*CYP2C19*	Consider alternative antiplatelet therapy (for example, prasugrel or ticagrelor)
Thiopurine sensitivity	*TPMT*	Reduce thiopurine dosage or consider alternative agent
Codeine sensitivity	*CYP2D6*	Avoid use of codeine; consider alternatives such as morphine and non-opioid analgesics
Simvastatin sensitivity	*SLCO1B1*	Reduce dose of simvastatin or consider an alternative statin; consider routine creatine kinase surveillance

A: Mendelian disease refers to diseases which occur due to specific mutations in single genes, which are generally inherited from the parents. The same disease may occur through other pathways not involving the genes/mutations listed here, however, such as cystic fibrosis.

B: Precision oncology in this table refers to the genetic profiling of tumors in order to enable targeted treatments.

C: Pharmacogenomics refers to the use of an individual's genetic profile to predict their response to therapeutic drugs.

Source: Table derived from Euan A. Ashley, "Towards Precision Medicine," *Nature Reviews Genetics* 17, no. 9 (2016), https://www.nature.com/articles/nrg.2016.86#Sec4.

2. Diagnostics

The diagnostic process is defined as the process of identifying a disease, condition, or injury from its signs and symptoms.[9] A diagnostic procedure/technique is one that can help diagnose a disease or condition. In this document, diagnostics that relate to chemical and/or biological agents are considered. Due to the nature of precision medicine, diagnostics technologies in this document are not limited to diagnosing a disease or condition, but also include technologies that can extract

[9] "NCI Dictionary of Cancer Terms," National Cancer Institute Website, accessed August 25, 2022, https://www.cancer.gov/publications/dictionaries/cancer-terms/expand/D.

information about the nature and state of a disease and/or individual. An example would be next-generation sequencing (NGS) technologies, which can be used both for diagnosing infections and for identifying host genetic variation altering susceptibility to disease. This concept is expanded upon in the following section.

3. Relevance of Precision Medicine to Diagnostics

Precision medicine is a multi-step process spanning multiple domains, such as the collection and processing of a large amount of data, selection of personalized drug dosages, and the development of analytical tools for monitoring clinical, genetic, and environmental parameters.[10] Biological and chemical diagnostics can play a role in the implementation of precision medicine concepts, for instance by the detection of biomarkers which may help predict a patient's disease progression. Sequencing technologies are another example, and can characterize a patient's genome to identify markers of risk. Various diagnostic technologies have analogous applications in the various omics domains, further demonstrating the overlap of diagnostic technologies and precision medicine (this is expanded upon in Section 3.1.b).

Precision medicine technology, when integrated with diagnostic systems, could have multiple advantages including increasing timeliness of diagnostic information and actionability to the warfighter and/or medical system. It is important to note that precision medicine is a concept that can be used in parallel with diagnostic technologies, rather than integrated into diagnostic technologies. Precision medicine concepts can alter diagnostic technologies in various ways, such as requiring the detection of biomarkers at different intervals or detecting novel biomarkers.

A large proportion of current precision medicine research work is directed at conditions such as cancer. This is a logical step; susceptibility to and progression of cancer is largely driven by an individual's own clinical attributes, including genetic makeup, immune system function, and epigenetic changes.[11] Cancer treatments are generally longer and more tailorable than other treatments, such as antibiotics for infections. As shown in the figure below representing a key-word search of the registered clinical trials on ClinicalTrials.gov, of all precision medicine clinical trials as of 2022, cancer-related trials made up the largest group, over-represented when compared to the overall proportion of registered trials. However, many precision medicine approaches may be transferable to detecting exposure to chemical/biological agents of interest and to diagnosis of the diseases they produce, and thus remain quite valuable.

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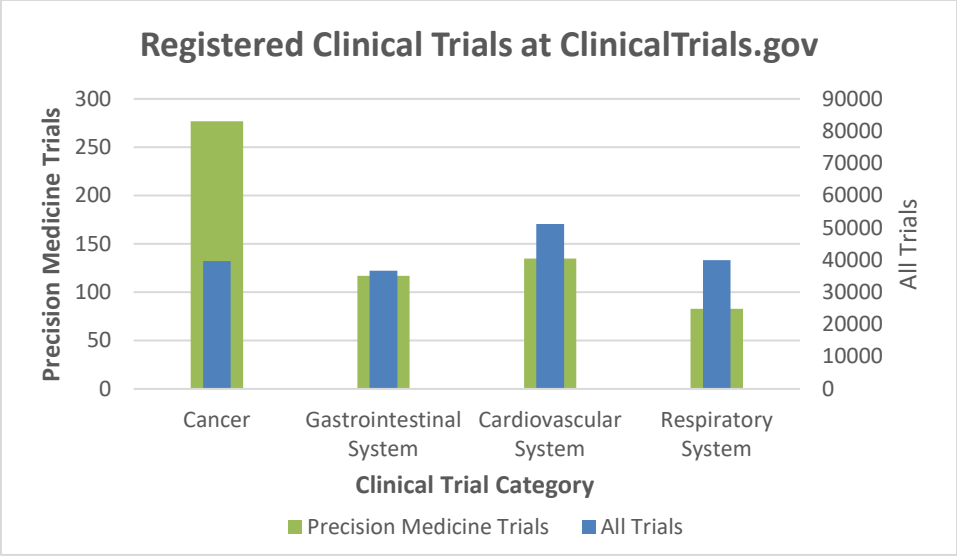
[10] Maria M. Calabretta et al., "Precision Medicine, Bioanalytics and Nanomaterials: Toward a New Generation of Personalized Portable Diagnostics," *Analyst* 145, no. 8 (2020), https://pubs.rsc.org/en/content/articlehtml/2020/an/c9an02041a.

[11] Paulina Krzyszczyk et al., "The Growing Role of Precision and Personalized Medicine for Cancer Treatment," *Technology* 6, 3-4 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6352312/.



Source: Derived from "ClinicalTrials.Gov," National Institutes of Health - U.S. National Library of Medicine Website, accessed September 5, 2022, https://www.clinicaltrials.gov/ct2/home.

Figure 1. Overview of Precision Medicine Trials Registered on ClinicalTrials.gov

B. Search Terms

We conducted a literature search using individual journals such as *Nature, PLOS One,* and *Science*, as well as databases such as PubMed and Google Scholar. To try and capture a large amount of studies, we used various combinations of search terms for each domain of interest. Generally, the search terms used included a combination of "precision medicine" and the domain of interest. Search terms for the omics portions of the study include combinations of "diagnostics," "CBRN," "biothreat," "chemical," "biological," "agent," "clinical," "infectious disease," along with the "omic" domain of interest.

The agent-specific search included a combination of the above search terms with the agent of interest. As different technologies were identified performing the literature review, they were analyzed in depth by performing searches, combining the search terms "diagnostics," "precision medicine," "CBRN," "biothreat," "chemical," "biological," "agent," "clinical," along with the technology of interest. All searches were limited to studies which were unclassified and publicly distributed.

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3. Integration with Diagnostic Technologies

Precision medicine is a concept of therapy, focused on improving clinical outcomes using data obtained from patients. There are no "precision medicine technologies," per se, but precision medicine concepts can be integrated into various technologies. Precision medicine concepts can alter diagnostic technologies in multiple ways, such as requiring the detection of different targets, requiring target detection at greater frequencies, or changes in data processing methods. The end goal of such changes would be to help modify medical interventions and preventive care, including better predictions of disease progression. However, this does not necessarily include improvements in making the diagnoses themselves.

Biomarkers are promising diagnostic tools for supporting precision medicine, but there are currently limited clinical results due to a "reliance on syndromic definitions and the lack of clear gold-standard diagnostics linked to pathophysiology."[12] With a range of interconnected symptoms typically associated with a disease, it can be difficult to identify a single biomarker that clearly and effectively defines a disease.[13] Multiple biomarkers may be simultaneously associated with a disease at different time points, severity levels, or different strains of the causative pathogen. A portfolio of associated biomarkers may provide a more complete diagnostic picture, but also introduces the potential for an overreliance on large numbers of specific (and costly) tests required for a single disease.[14]

In the context of precision medicine, this level of sensitivity and specificity in diagnostics may help with more accurate treatment plans that balance the risk and reward of certain therapeutics, including a patient's individual likelihood of responding to that treatment.[15] Because the efficacy of many therapeutics depends on the timeliness of administration, ensuring a clinically relevant timeline for intervention should be an important consideration in biomarker research.[16] Many of the techniques described here would not necessarily enable earlier detection of the agent, but could allow for earlier intervention by providing actionable data about disease progression.

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[12] Timothy E. Sweeney and Purvesh Khatri, "Generalizable Biomarkers in Critical Care: Toward Precision Medicine," *Critical Care Medicine* 45, no. 6 (2017): 934, https://doi.org/10.1097/CCM.0000000000002402.

[13] Ibid, 934.

[14] Ibid, 935.

[15] Thomas M. Kuntz and Jack A. Gilbert, "Introducing the Microbiome into Precision Medicine," *Trends in Pharmacological Sciences* 38, no. 1 (2017): 81, https://doi.org/10.1016/j.tips.2016.10.001.

[16] Sweeney and Khatri, "Generalizable Biomarkers in Critical Care: Toward Precision Medicine," 937.

A. Diagnostic Targets

All precision medicine strategies include the use of decision-making processes based on various underlying data. Future personalized health care is expected to benefit from combined omics data, which includes not only genomic information but also the longitudinal documentation of all possible molecular and clinical components.[17] This could be epigenetic modifications of the genome, RNA transcripts, translated proteins, the genetic material of non-human organisms associated with human environments, metabolites, and clinical characteristics of an individual.

1. Genome

The identification of various features of an individual's genome can allow for predictions of an individual's response to different stimuli, including pathogens. These features (variants) may be in multiple forms, such as single nucleotide variations, insertions, deletions, or structural variations. The modern definition of genomics also includes pharmacogenomics, which goes beyond characterization of disease into characterization of response to various therapeutics. Genomics technologies do not have to be limited to just an individuals' genetic makeup; it can also include the genetic information of diverse micro-organisms residing on or within an individual. This domain of metagenomics is described in the section on the microbiome (3.1.b.4)).

Genetic technologies have been essential for enacting precision medicine concepts, especially in diseases such as cystic fibrosis and cancer. This has improved patient outcomes by targeting treatments to specific subpopulations, with a better characterization of pathologies. Genetic diagnostics employ various strategies that target different portions of the genome (e.g., whole genome sequencing, exome sequencing), including different methods of extracting genomic information (e.g., short read sequencing, long read sequencing).

For many diseases, the use of genetic markers to guide clinical decisions has become commonplace. For example, associations of HLA-C*06:02 with biologic therapy response in psoriasis,[18] and HLA-DRB1 with treatment response in rheumatoid arthritis.[19] HLA alleles have been implied by many genome-wide association studies (GWAS) to be associated with autoimmune diseases and other non-communicable diseases, with population-specific variants

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[17] Rui Chen and Michael Snyder, "Promise of Personalized Omics to Precision Medicine," *Wiley Interdisciplinary Reviews. Systems Biology and Medicine* 5, no. 1 (2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154620/.

[18] Nick Dand et al., "HLA-C*06:02 Genotype Is a Predictive Biomarker of Biologic Treatment Response in Psoriasis," *The Journal of Allergy and Clinical Immunology* 143, no. 6 (2019), https://doi.org/10.1016/j.jaci.2018.11.038.

[19] Sebastien Viatte et al., "Association of HLA-DRB1 Haplotypes with Rheumatoid Arthritis Severity, Mortality, and Treatment Response," *JAMA* 313, no. 16 (2015), https://doi.org/10.1001/jama.2015.3435.

having significant effects on diseases such as osteoarthritis[20] or type 2 diabetes.[21] Genome-wide association studies are a type of observational study in which a genome-wide set of genetic variants are observed in multiple individuals, in order to establish associations between variants and traits, thus making them an essential part of precision medicine.

Precision medicine concepts have been widely used to select drugs effective against certain types of cancers. For example, breast cancer which is positive for the human epidermal growth factor receptor 2 (HER2) is associated with increased effectiveness of drugs such as trastuzumab, lapatinib, and pertuzumab when used in conjunction with traditional chemotherapy.[22,23,24]

Identified associations also make it possible to assign risk scores to individuals, in order to identify individuals at higher risk of disease. This can help make clinical decisions to improve outcomes, including more aggressive interventions. These associations do not necessarily have to be limited to a single nucleotide polymorphism (SNP) or allele, and may include multiple features from an individual's genome. For instance, one paper found that a polygenic panel could act as a predictor for an individual's risk for five common diseases (coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer).[25]

Genetic technologies associated with precision medicine also benefit the treatment of infectious diseases, with a large number of studies having been performed after the beginning of the SARS-CoV-2 pandemic. An analysis of 49,562 COVID-19 patients from 46 studies identified 13 significant loci associated with severe SARS-CoV-2 infection, with some of the identified loci also corresponding to other disease associations such as autoimmune or inflammatory diseases.[26,27] Some other associations identified are highlighted in Section 3.2.g.

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[20] Unnur Styrkarsdottir et al., "Whole-Genome Sequencing Identifies Rare Genotypes in COMP and CHADL Associated with High Risk of Hip Osteoarthritis," *Nature Genetics* 49, no. 5 (2017), https://doi.org/10.1038/ng.3816.

[21] Ida Moltke et al., "A Common Greenlandic TBC1D4 Variant Confers Muscle Insulin Resistance and Type 2 Diabetes," *Nature* 512, no. 7513 (2014), https://doi.org/10.1038/nature13425.

[22] Charles E. Geyer et al., "Lapatinib Plus Capecitabine for HER2-Positive Advanced Breast Cancer," *The New England Journal of Medicine* 355, no. 26 (2006), https://pubmed.ncbi.nlm.nih.gov/17192538/.

[23] D. J. Slamon et al., "Use of Chemotherapy Plus a Monoclonal Antibody Against HER2 for Metastatic Breast Cancer That Overexpresses HER2," *The New England Journal of Medicine* 344, no. 11 (2001), https://pubmed.ncbi.nlm.nih.gov/11248153/.

[24] Sandra M. Swain et al., "Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer," *The New England Journal of Medicine* 372, no. 8 (2015), https://doi.org/10.1056/NEJMoa1413513.

[25] Amit V. Khera et al., "Genome-Wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations," *Nature Genetics* 50, no. 9 (2018), https://doi.org/10.1038/s41588-018-0183-z.

[26] David Ellinghaus et al., "Genomewide Association Study of Severe Covid-19 with Respiratory Failure," *The New England Journal of Medicine* 383, no. 16 (2020), https://doi.org/10.1056/NEJMoa2020283.

[27] COVID-19 Host Genetics Initiative, "Mapping the Human Genetic Architecture of COVID-19," *Nature* 600, no. 7889 (2021), https://www.nature.com/articles/s41586-021-03767-x.

Genetic testing does not have to be limited to host-based testing, and testing of the biological agent itself may arguably be included in the definition of precision medicine, given that this information can be used to guide clinical decisions based on features such as antibiotic resistance. Many of the state-of-the-art technologies to diagnose infectious diseases and characterize them based on their characteristics are analyzed in IDA Paper P-33049, and are directly relevant to precision medicine implementations.[28] For instance, CRISPR-dCas9 is a novel technology which has been used to detect antibiotic resistance by recognizing antibiotic resistance genes, with ultra-sensitive and rapid detection capabilities, without the requirement of heavy instruments.[29]

Whole-genome sequencing (WGS) strategies attempt to sequence the entire genome, without focusing on specific regions of interest. As sequencing technologies rapidly develop, WGS is becoming more and more viable as a diagnostic assay. However, to avoid the difficulties in having to sequence and process large amounts of data, techniques concentrating on selected areas of the genome have become commonplace. The enrichment of selected areas of the genome, usually by hybridization to known sequences, is termed as *capture*.[30]

Techniques like exome sequencing focus only on the capture of exomes (i.e., the parts of the genome which contain exons, the coding portions of genes) in order to prevent having to analyze the entire genome. Augmented exome sequencing uses extra probes in both coding and non-coding regions in order to augment coverage, along with other methods such as targeted polymerase chain reaction (PCR) to fill in gaps. Augmented exome sequencing may have some disadvantages, as regions rich in the nucleotides (GC-rich regions) usually cannot be optimized by simply expanding coverage using the aforementioned techniques, usually requiring sequencing conditions tailored to their chemistry.[31]

The advantages of augmented exome sequencing when the target region is clearly defined is demonstrated in the case of the KCNH2 gene, in a paper published by a researcher at the Center for Inherited Cardiovascular Disease, Stanford Medicine.[32] "Coverage" refers to the number of times a single base is sequenced during a nucleotide sequencing assay. The KCNH2 gene represents a scenario where WGS provides even coverage of the coding region of the gene, but at a coverage which may not be clinically sufficient. The standard exome panel results in higher but

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[28] Catherine Scheible et al., Analysis of State-of-the-Art Diagnostics for Far-Forward Use, IDA Paper P-33049, (Alexandria, VA: Institute for Defense Analyses, July 2022).

[29] Vilhelm Müller et al., "Direct Identification of Antibiotic Resistance Genes on Single Plasmid Molecules Using CRISPR/Cas9 in Combination with Optical DNA Mapping," *Scientific Reports* 6, no. 1 (2016), https://www.nature.com/articles/srep37938.

[30] Euan A. Ashley, "Towards Precision Medicine," *Nature Reviews Genetics* 17, no. 9 (2016), https://www.nature.com/articles/nrg.2016.86#Sec4.

[31] Anil Patwardhan et al., "Achieving High-Sensitivity for Clinical Applications Using Augmented Exome Sequencing," *Genome Medicine* 7, no. 1 (2015), https://link.springer.com/article/10.1186/s13073-015-0197-4.

[32] Euan A. Ashley, "Towards Precision Medicine," *Nature Reviews Genetics* 17, no. 9 (2016), https://www.nature.com/articles/nrg.2016.86#Sec4.

highly variable coverage, while augmented exome capture can target medically relevant areas and fill in gaps for consistent, high coverage, and would be the most suitable for detecting variants in this gene in this scenario. Depending on the use-case, either of these strategies may be applicable, and must be considered when performing nucleotide sequencing to generate data for precision medicine.

There have been rapid advancements in the field of genetic sequencing, especially with the introduction of "next-generation sequencing" (NGS) technologies around 2004-2006.[33] The cost of sequencing has drastically decreased over time, outpacing Moore's law since 2001.[34] Along with the increase in direct sequencing technologies which allowed massively parallel sequencing of individual DNA molecules, the procedures involved with processing sequencing data also evolved.

NGS sequencing, also known as second-generation technologies, generally involve massively parallel sequencing of "short-reads." The term "massively parallel" is used as the sequencing methods involve individual, spatially separated reactions, and therefore multiple sequences are processed in parallel. They are also described as "short-read" methods as each read (i.e., the size of each DNA fragment sequenced) is in the range of 250-800 base pairs. Because of this low read length, assembling the sequenced data presents additional challenges, especially in regions with structural features such as repeats.

Different organizations depend on different sequencing technologies. Illumina's NGS technology is based on sequencing-by-synthesis (SBS), with a fluorescent-labeled reversible terminator technology.[35] The technology detects single bases as they are incorporated into growing DNA strands, in order to identify the sequence of interest. The Illumina MiSeq instrument, commonly used for clinical HLA typing, favors fragments 350-500 bases long.[36] Illumina has the most accurate base-by-base sequencing technology on the market, with an error rate of ~0.1 percent.[37] Ion Torrent's platform works by clonal amplification, using a bead-by-bead method of particles in a micro-well using emulsion PCR. Adapter sequences are ligated to DNA fragments, captured in an emulsion droplet, and after amplification, nucleotide incorporation results in release

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33 Taishan Hu et al., "Next-Generation Sequencing Technologies: An Overview," *Human Immunology* 82, no. 11 (2021), https://www.sciencedirect.com/science/article/pii/S0198885921000628.

34 "DNA Sequencing Costs: Data," National Human Genome Research Institute Website, accessed November 14, 2022, https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data.

35 Elaine R. Mardis, "Next-Generation Sequencing Platforms," *Annual Review of Analytical Chemistry* 6 (2013), https://doi.org/10.1146/annurev-anchem-062012-092628.

36 Manish J. Gandhi et al., "Targeted Next-Generation Sequencing for Human Leukocyte Antigen Typing in a Clinical Laboratory: Metrics of Relevance and Considerations for Its Successful Implementation," *Archives of Pathology & Laboratory Medicine* 141, no. 6 (2017), https://doi.org/10.5858/arpa.2016-0537-RA.

37 Hu et al., "Next-Generation Sequencing Technologies: An Overview."

of hydrogen ions which can be detected by pH sensors.[38] 454 Pyrosequencing, currently discontinued, was also a common method for genome sequencing, based on the detection of pyrophosphate, a biproduct of nucleotide incorporation, in order to detect whether a particular base had been incorporated in a DNA chain.[39]

Long-read technologies, also called third-generation sequencing technologies, generally produce reads >10kb in length. Long reads can overcome many of the difficulties of short reads in regards to genome assembly, especially when dealing with repetitive sequences. Two of the primary long-read technologies are currently developed by Pacific Biosciences (PacBio) and Oxford Nanopore Technology.[40] PacBio's sequencing, the Single Molecule Real-Time (SMRT) sequencing method, consists of generation of a circular DNA template from the target DNA using ligation of hairpin adapters to both ends of the DNA molecule. Sequencing occurs in a "SMRT cell" chip, where many pores called zero-mode waveguides (ZMW) immobilize individual DNA polymerase molecules. Fluorescently labelled nucleotides with unique emission spectra are used, enabling the detection of light pulses which can be translated into a nucleotide sequence. Oxford Nanopore, on the other hand, can produce raw sequence reads >1Mb in length. Their method is based on the passage of a single-stranded nucleic acid molecule through a protein pore.[41] The detection of changes in an applied ion current as the strand moves through the pore allows for detection of the nucleotide sequence.

2. Multi-omics

Beginning with traditional genomics, the development of various biological technologies has created the field of "omics," which refers to the comprehensive study of the roles, relationships, and actions of various types of molecules and cells in an organism.[42] This includes fields like transcriptomics, proteomics, and metabolomics, among others. Non-genomics omics technologies have now been applied across the various spectrum of human disorders. The subsequent sections provide an introduction to various omics domains, describing how diagnostic technologies are implemented for the application of precision medicine concepts in each domain.

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38 Mardis, "Next-Generation Sequencing Platforms."

39 Barton E. Slatko, Andrew F. Gardner, and Frederick M. Ausubel, "Overview of Next-Generation Sequencing Technologies," *Current Protocols in Molecular Biology* 122, no. 1 (2018), https://doi.org/10.1002/cpmb.59.

40 Hu et al., "Next-Generation Sequencing Technologies: An Overview."

41 James Clarke et al., "Continuous Base Identification for Single-Molecule Nanopore DNA Sequencing," *Nature Nanotechnology* 4, no. 4 (2009), https://www.nature.com/articles/nnano.2009.12.

42 Michael Olivier et al., "The Need for Multi-Omics Biomarker Signatures in Precision Medicine," *International Journal of Molecular Sciences* 20, no. 19 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6801754/.

a. Epigenome

The epigenome refers to the complete description of all chemical modifications to DNA and histone proteins, which form a network that modulates chromatin structure and genome function.[43] The main types of epigenetic marks are DNA methylation, histone modifications, microRNAs (miRNAs), non-coding RNAs (ncRNAs) and long noncoding RNAs (lnRNAs) expression, and chromatin condensation; however, other modifications also exist.[44]

Epigenetic modifications are considered to be a link between the genome and the environment, providing important targets and biomarkers for personalized medicine.[45] Epigenetic changes have various functions in the cell, with a major function being the regulation of gene expression by altering the accessibility of chromatin to transcription factors. For instance, methylation of DNA mainly occurs in the cytosine-paired-with-guanine (CpG) dinucleotide sequences, which then physically impedes the binding of transcription factors to DNA or preventing recognition of methylated sites by chromatin-modifying enzymes. This prevents transcription from occurring and reduces gene expression.

Epigenome-wide association studies have allowed for characterizations of disease, which could improve diagnoses and prognoses.[46] An epigenetic study of COVID-19 severity uncovered 44 CpG sites which were associated with disease severity, many of which were also associated with the native interferon response to viral infection.[47] Markers like these can be used in order to identify high-risk patients for observation and earlier/aggressive treatments.

Identifying the host methylation profile can also predict clinical outcome of COVID-19, as demonstrated in a longitudinal study of 164 patients performed by Konigsberg et al.[48] The study used machine learning techniques in order to build a prediction system, and could successfully predict characteristics such as hospitalization, ICU admission, and progression to death due to COVID-19. This is a direct example of how epigenetics can be used to implement diagnostic targets. The detection of an individual's epigenetic profile through the various technologies listed in Table 2 can allow for clinical predictions, which can ultimately lead to medical decisions to improve patient outcome. This concept can be extended to other infectious diseases as well, but

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[43] Bradley E. Bernstein, Alexander Meissner, and Eric S. Lander, "The Mammalian Epigenome," *Cell* 128, no. 4 (2007), https://www.sciencedirect.com/science/article/pii/S0092867407001286.

[44] Anna Portela and Manel Esteller, "Epigenetic Modifications and Human Disease," *Nature Biotechnology* 28, no. 10 (2010), https://www.nature.com/articles/nbt.1685.

[45] Wang et al., "Toward Multiomics-Based Next-Generation Diagnostics for Precision Medicine."

[46] Epigenome-wide association studies are analogous to genome-wide association studies (GWAS), instead using the epigenome instead of the genome to identify associations for various traits.

[47] Manuel Castro de Moura et al., "Epigenome-Wide Association Study of COVID-19 Severity with Respiratory Failure," *eBioMedicine* 66 (2021), https://www.sciencedirect.com/science/article/pii/S2352396421001328.

[48] Iain R. Konigsberg et al., "Host Methylation Predicts SARS-CoV-2 Infection and Clinical Outcome," *Communications Medicine* 1, no. 1 (2021), https://doi.org/10.1038/s43856-021-00042-y.

research is still required to identify such associations for other diseases, and subsequently develop clinical decision-making systems such as patient classifiers.

Epigenetic markers may be transient but can also be inherited through cell division. This is in contrast to genetics, where inheritance is virtually perfect. Epigenetic changes hold the potential to cause diseases (epigenetic deregulation, i.e., epimutations), and also play a factor in the outcome of various diseases.[49] For example, genomic imprinting, a form of inheritance in which gene expression is based on the parent-of-origin (i.e., allele of only one parent is expressed), has been associated with modified risk of various diseases including cancers.[50] A well-known example of imprinting is a deletion in the q-arm of human Chromosome 15 – a maternal deletion leads to Angelman's Syndrome, while a paternal deletion leads to Prader-Willi syndrome.[51]

Multiple strategies exist for analyzing the epigenome, which vary based on characteristics such as throughput capability, resolution, and nature of target.[52] Different methods are required for the analysis of detection of different types of epigenetic modifications, each providing different advantages. Some of these are expanded upon in Table 2.

[49] Dana C. Dolinoy and Randy L. Jirtle, "Environmental Epigenomics in Human Health and Disease," *Environmental and Molecular Mutagenesis* 49, no. 1 (2008), https://doi.org/10.1002/em.20366.

[50] Dolinoy and Jirtle, "Environmental Epigenomics in Human Health and Disease."

[51] Louisa Kalsner and Stormy J. Chamberlain, "Prader-Willi, Angelman, and 15q11-q13 Duplication Syndromes," *Pediatric Clinics of North America* 62, no. 3 (2015): 587-606, https://pubmed.ncbi.nlm.nih.gov/26022164/.

[52] Yuanyuan Li, "Modern Epigenetics Methods in Biological Research," *Methods* 187 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7785612.

Table 2. Techniques for Epigenetic Analyses

Method	Modification Detected	Advantages	Disadvantages
PCR-based Bisulfite Sequencing[53]	DNA Methylation	Low cost, single-base resolution	Inconsistent results, may require multiple runs to confirm results
Methylation-specific PCR[54]	DNA Methylation	Low cost, single-base resolution	Not all CpG sites can be detected, low throughput
Pyrosequencing[55]	DNA Methylation	Accurate resolution, low cost, single-base resolution	Requires validated primers, prone to errors due to DNA degradation
Whole-Genome Bisulfite Sequencing[56]	DNA Methylation	Single-base resolution, can detect almost every CpG site	High cost, requires large amounts of input DNA, computationally expensive
HumanMethylation450 (Methylation 450K)[57]	DNA Methylation	Cost effective, single-base resolution	Coverage highly dependent on predesigned array
Methylation-sensitive Restriction Enzyme Bisulfite Sequencing[58]	DNA Methylation	Low cost, no dangerous chemicals used (safe)	Coverage depends on restriction enzyme sites, low resolution
ELISA-based assays[59]	DNA Methylation	Low cost, commercially available kits	Low resolution, high variability in results
Single-cell bisulfite sequencing[60]	DNA Methylation	High resolution, de novo methylation exploration	High cost, computationally expensive
SMRT Sequencing[61]	DNA Methylation	No harsh bisulfite treatment (safe), high coverage	Large amounts of input DNA needed, higher accuracy in bacterial genomes
Nanopore sequencing[62]	DNA Methylation	No harsh bisulfite treatment (safe), de novo exploration	Large amount of input DNA required, Computationally expensive
OxBS-seq[63]	DNA Methylation	High accuracy for evaluation of global 5hmC status	High amount of input DNA required, high-sequencing depth required
ChIP-PCR[64]	Histone Modifications	Standard method for detection of specific histone modifications, low cost	Only detects enrichment abundance, low-resolution
ChIP-chip[65]	Histone Modifications	De novo exploratory studies possible, low cost	Quality is dependent on antibody quality, prone to artifacts
ELISA-based assays[66]	Histone Modifications	Low cost, commercial kits available	Low resolution, high variability
qRT-PCR[67]	ncRNA	Commercial kits available, low cost, high sensitivity and specificity	Requires validated primers, requires annotations
RNA-seq[68]	ncRNA	Can analyze whole genome, high-resolution	Low sensitivity, high cost, computationally expensive
HITS-CLIP[69]	ncRNA	Single-base resolution, identifies interaction of ncRNA with specific proteins	High cost, low sensitivity, requires high quality antibodies, computationally expensive
Methyl-HiC[70]	Chromosome conformation	Simultaneous capture of DNA methylation and chromosome conformation	High cost, complicated procedure, computationally expensive

Source: Derived from Yuanyuan Li, "Modern Epigenetics Methods in Biological Research," *Methods* 187 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7785612.

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[53] Yuanyuan Li and Trygve O. Tollefsbol, "DNA Methylation Detection: Bisulfite Genomic Sequencing Analysis," *Methods in Molecular Biology* 791 (2011), https://link.springer.com/protocol/10.1007/978-1-61779-316-5_2.

[54] Keith Rand et al., "Conversion-Specific Detection of DNA Methylation Using Real-Time Polymerase Chain Reaction (ConLight-MSP) To Avoid False Positives," *Methods* 27, no. 2 (2002), https://doi.org/10.1016/S1046-2023(02)00062-2.

[55] Colin Delaney, Sanjay K. Garg, and Raymond Yung, "Analysis of DNA Methylation by Pyrosequencing," *Methods in Molecular Biology* 1343 (2015), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772880/.

[56] Magali Kernaleguen et al., "Whole-Genome Bisulfite Sequencing for the Analysis of Genome-Wide DNA Methylation and Hydroxymethylation Patterns at Single-Nucleotide Resolution," in *Epigenome Editing* (New York, NY: Humana Press, 2018).

[57] Sarah Dedeurwaerder et al., "Evaluation of the Infinium Methylation 450K Technology," *Epigenomics* 3, no. 6 (2011), https://pubmed.ncbi.nlm.nih.gov/22126295/.

[58] Giancarlo Bonora et al., "DNA Methylation Estimation Using Methylation-Sensitive Restriction Enzyme Bisulfite Sequencing (MREBS)," *PLoS ONE* 14, no. 4 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448829/.

[59] "The Enzyme-Linked Immunosorbent Assay (ELISA)," *Bulletin of the World Health Organization* 54, no. 2 (1976), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2366430.

[60] Omer Schwartzman and Amos Tanay, "Single-Cell Epigenomics: Techniques and Emerging Applications," *Nature Reviews Genetics* 16, no. 12 (2015), https://www.nature.com/articles/nrg3980.

[61] Quentin Gouil and Andrew Keniry, "Latest Techniques to Study DNA Methylation," *Essays in Biochemistry* 63, no. 6 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6923321/.

[62] Andrew H. Laszlo et al., "Detection and Mapping of 5-Methylcytosine and 5-Hydroxymethylcytosine with Nanopore MspA," *Proceedings of the National Academy of Sciences of the United States of America* 110, no. 47 (2013), https://doi.org/10.1073/pnas.1310240110.

[63] Michael J. Booth et al., "Oxidative Bisulfite Sequencing of 5-Methylcytosine and 5-Hydroxymethylcytosine," *Nature Protocols* 8, no. 10 (2013), https://doi.org/10.1038/nprot.2013.115.

[64] Padmaja Gade and Dhan V. Kalvakolanu, "Chromatin Immunoprecipitation Assay as a Tool for Analyzing Transcription Factor Activity," *Methods in Molecular Biology* 809 (2012), https://doi.org/10.1007/978-1-61779-376-9_6.

[65] Smitha Pillai and Srikumar P. Chellappan, "ChIP on Chip Assays: Genome-Wide Analysis of Transcription Factor Binding and Histone Modifications," *Methods in Molecular Biology* 523 (2009), https://doi.org/10.1007/978-1-59745-190-1_23.

[66] "The enzyme-linked immunosorbent assay (ELISA)."

[67] Colin C. Pritchard, Heather H. Cheng, and Muneesh Tewari, "MicroRNA Profiling: Approaches and Considerations," *Nature Reviews Genetics* 13, no. 5 (2012), https://www.nature.com/articles/nrg3198.

[68] Mei Cao, Jian Zhao, and Guoku Hu, "Genome-Wide Methods for Investigating Long Noncoding RNAs," *Biomedicine and Pharmacotherapy* 111 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6401243/.

[69] Sung W. Chi et al., "Argonaute HITS-CLIP Decodes MicroRNA-MRNA Interaction Maps," *Nature* 460, no. 7254 (2009), https://doi.org/10.1038/nature08170.

[70] Guoqiang Li et al., "Joint Profiling of DNA Methylation and Chromatin Architecture in Single Cells," *Nature Methods* 16, no. 10 (2019), https://doi.org/10.1038/s41592-019-0502-z.

b. Transcriptome

The transcriptome is the complete set of RNA transcripts in a cell or tissue of interest, which can include rRNAs, mRNAs, tRNAs, and miRNAs, among others.[71] Various methods of RNA sequencing (RNA-seq) can reveal the features of the transcriptome, up to a single-cell resolution (scRNA-seq).[72] ncRNAs may also be associated with epigenetic modifications due to their interactions with DNA, and therefore some methods of ncRNA analyses have been mentioned in Section 3.1.b.1).

The transcriptome may be a useful tool for early detection or screening for a biological agent. In 2005, the U.S. military performed the first in vivo demonstration of classification of infectious disease by the host transcriptome, using transcriptomics to differentiate febrile respiratory illnesses (FRIs) caused by adenoviruses against other causes.[73] The study used a transcriptome panel which included interferon-induced genes, complement cascades, and TNF and IL1 signaling transcripts to create a patient classification tool. Such tools could be adapted for various diseases, and can act as both a diagnostic tool as well as infectious disease surveillance tool.

The viral load in the early stage of disease after infection is low in various diseases such as infections with the Ebola Virus (EBOV) and the Marburg Virus (MARV). Moreover, the virus accumulates in the blood only after significantly replicating in organs such as the liver and spleen.[74] This makes diagnosis difficult via traditional methods that rely on the detection of viral particles. In an attempt to use transcriptomics for earlier identification of disease, one study created a tool combining viral RNA detection with sentinel host mRNA detection following filovirus detection. Tested in non-human primates, the approach could distinguish the causative agent (EBOV and MARV) samples in the pre-viremic stage. This approach may be transferred to different viral and bacterial infections, potentially allowing for pre-symptomatic diagnosis. This may be a valuable source of information useful in biological surveillance, and could help in making clinical decisions such as allowing for earlier quarantine of exposed persons.

Studies similar to the one mentioned above have been successful in using the host transcriptome to characterize disease, including differentiating viral from bacterial infection and identifying interferon-stimulated genes (ISG) markers, which are differentially regulated in early

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71 Mihaela Pertea, "The Human Transcriptome: An Unfinished Story," *Genes* 3, no. 3 (2012), https://www.mdpi.com/2073-4425/3/3/344/htm.

72 Rebecca A. Ward et al., "Harnessing the Potential of Multiomics Studies for Precision Medicine in Infectious Disease," *Open Forum Infectious Diseases* 8, no. 11 (2021), https://academic.oup.com/ofid/article/8/11/ofab483/6375269.

73 D. C. Thach et al., "Surveillance of Transcriptomes in Basic Military Trainees with Normal, Febrile Respiratory Illness, and Convalescent Phenotypes," *Genes & Immunity* 6, no. 7 (2005), https://www.nature.com/articles/6364244#Sec9.

74 Emily Speranza et al., "Previremic Identification of Ebola or Marburg Virus Infection Using Integrated Host-Transcriptome and Viral Genome Detection," *mBio* 11, no. 3 (2020), https://doi.org/10.1128/mBio.01157-20.

viral infection.[75,76] These diagnostic tools are not limited to viral infections, and marker classifier panels have been created that can distinguish *B. pseudomallei* infection from other sepsis-causing agents.[77] Exosomal miRNAs have also been used to identify active pulmonary tuberculosis.[78] Future work would be required to expand these tools to other agents, and to identify the specificity of such tools. The markers used for transcriptomic analyses may also be expressed in other situations, and extensive testing is thus required to characterize host responses adequately.

The use of transcriptomics also extends to predicting clinical outcomes, as the gene expression profile of an individual can provide information about the state of disease. *For B. pseudomallei*, one study found that the host transcriptome was a good indicator of 28-day mortality, which would be useful in urgent care scenarios where the initial clinical presentation of a patient may not accurately reflect the patient's clinical course.[79] The host transcriptomic profile could also act as an indicator of treatment effectiveness. Over a course of oseltamivir in influenza patients, it was demonstrated that the host transcriptomic signature changed throughout treatment, returning to a baseline after recovery.[80]

There also appears to be a large potential role for transcriptomics in the management of sepsis. Sepsis is a large challenge faced by the U.S. military; about 25 percent of the deaths from otherwise survivable injuries in operations Iraqi and Enduring Freedom were attributed to sepsis.[81] Characterization of sepsis is clinically difficult, with severe combat injuries causing nonspecific clinical presentations of inflammatory responses following trauma.[82]

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75 Christopher W. Woods et al., "A Host Transcriptional Signature for Presymptomatic Detection of Infection in Humans Exposed to Influenza H1N1 or H3N2," *PLoS ONE* 8, no. 1 (2013), https://doi.org/10.1371/journal.pone.0052198.

76 Aimee K. Zaas et al., "A Host-Based RT-PCR Gene Expression Signature to Identify Acute Respiratory Viral Infection," *Science Translational Medicine* 5, no. 203 (2013), https://doi.org/10.1126/scitranslmed.3006280.

77 Kevin L. Schully and Danielle V. Clark, "Chapter 8 - Aspiring to Precision Medicine for Infectious Diseases in Resource Limited Settings," in *Genomic and Precision Medicine: Infectious and Inflammatory Disease,* ed. Geoffrey S. Ginsburg et al., 3rd (Amsterdam: Academic Press, 2019), https://www.sciencedirect.com/science/article/pii/B9780128014967000083.

78 Shamila D. Alipoor et al., "Serum Exosomal MiRNAs Are Associated with Active Pulmonary Tuberculosis," *Disease Markers* 2019 (2019), https://doi.org/10.1155/2019/1907426.

79 Schully and Clark, "Chapter 8 - Aspiring to precision medicine for infectious diseases in resource limited settings."

80 Micah T. McClain et al., "A Genomic Signature of Influenza Infection Shows Potential for Presymptomatic Detection, Guiding Early Therapy, and Monitoring Clinical Responses," *Open Forum Infectious Diseases* 3, no. 1 (2016), https://doi.org/10.1093/ofid/ofw007.

81 John B. Holcomb et al., "Causes of Death in U.S. Special Operations Forces in the Global War on Terrorism: 2001-2004," *Annals of Surgery* 245, no. 6 (2007), https://doi.org/10.1097/01.sla.0000259433.03754.98.

82 Brian K. Hogan et al., "Correlation of American Burn Association Sepsis Criteria with the Presence of Bacteremia in Burned Patients Admitted to the Intensive Care Unit," *Journal of Burn Care & Research* 33, no. 3 (2012): 371-78, https://doi.org/10.1097/BCR.0b013e3182331e87.

The first Food and Drug Administration (FDA)-approved RNA biomarker diagnostic tool, SeptiCyte LAB, was designed to discriminate between sepsis and infection-negative inflammation in critically ill patients.[83] Novel transcriptomic sepsis classifiers have also been developed, including one which uses unsupervised clustering to classify sepsis into different mechanistic endotypes.[84] These endotypes could then suggest application of different therapies (e.g. patients with the NPS endotype, or Neutrophilic Suppressive, would be offered immune-recovering therapies such as interferon gamma or GM-CSF), and patients with the INF endotype (Interferon) might benefit from a focus on anti-inflammatory therapies.

A similar study identifying the subclasses of septic shock in patients with pneumopathies identified 117 differentially expressed genes; the most significant were the MME and THBS1 genes with an AUC of 0.879 and 0.889, respectively.[85] The identified genes provide an insight into the pathways of septic shock with pneumopathies, and can help establish prognosis of septic shock patients by identifying high-risk individuals.

There have not been a large amount of transcriptomic studies performed for infectious diseases to date; however, there has been a recent push for transcriptomic analyses. The UK Health Security Agency and Liverpool University have started a three-year project to compare responses to the Ebola Virus in humans and animals, identifying biomarkers of disease progression and correlating host response with disease pathology.[86]

It has also been found that transcriptomic signatures, or "transfer signatures" can be common across species, enabling the use of animal transcriptomic data to guide human studies.[87] This approach was tested using the progression of latent tuberculosis to active tuberculosis, and in identifying the severity of COVID-19 and H1N1 infections. Further studies could allow for transcriptomic diagnostics to act as broad-spectrum diagnostics, identifying diseases based on differential gene expression.

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83 Leo McHugh et al., "A Molecular Host Response Assay to Discriminate Between Sepsis and Infection-Negative Systemic Inflammation in Critically Ill Patients: Discovery and Validation in Independent Cohorts," *PLOS Medicine* 12, no. 12 (2015), https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001916.

84 Arjun Baghela et al., "Predicting Sepsis Severity at First Clinical Presentation: The Role of Endotypes and Mechanistic Signatures," *EBioMedicine* 75 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8808161/.

85 Songchang Shi et al., "Identification of Transcriptomics Biomarkers for the Early Prediction of the Prognosis of Septic Shock from Pneumopathies," *BMC Infectious Diseases* 21, no. 1 (2021), https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-06888-w.

86 *"*Comparison of Host Responses to Ebola Virus Disease (EVD)," U.S. Food and Drug Administration Website, accessed September 16, 2022, https://www.fda.gov/emergency-preparedness-and-response/mcm-regulatory-science/comparison-host-responses-ebola-virus-disease-evd.

87 Julia Di Iulio et al., "Transfer Transcriptomic Signatures for Infectious Diseases," *Proceedings of the National Academy of Sciences of the United States of America* 118, no. 22 (2021), https://doi.org/10.1073/pnas.2022486118.

c. Proteome

The proteome consists of the complete protein makeup of a cell or tissue in a defined condition. Proteins are chains of amino acids, which result from the process of translation from RNA templates and represent gene expression. Beyond simple gene expression, proteins can be processed to modify their amino acid constituents and can take different structural conformations or interact with other molecules to form complexes, all of which are examples of data that can be included in the proteome.[88] Multiple protein biomarkers have been identified that can provide information about pathologies and assist in clinical decision making. The proteome consists of the sum of all proteins, but proteomics technologies can be used to analyze a small subset of proteins, or even individual proteins, some of which are discussed here.

Many proteomics-based diagnostic assays are already in use for various conditions, such as the use of mass spectrometry for the detection of apolipoprotein-B-to-apolipoprotein-A1 ratios, used in cardiovascular disease management.[89] Proteomics pipelines for sample analyses have also improved significantly in the past decade, with developments including automated mass spectrometry sample preparation to produce tryptic peptides, improved sensitivity, and improved software algorithms.[90] Longitudinal proteomic analyses of individuals can also provide accumulated risk measurements, helping to quantify interindividual variability in baseline proteomes. In this way, longitudinal characterization of an individual's proteome could allow for early diagnoses of disease, and also allow for tracking and prediction of clinical progression.

An example of an application of proteomics for precision medicine is the TRIAGE study.[91] This study measured the performance of three candidate biomarkers (proadrenomedullin (ProADM), copeptin, and procalcitonin (PCT)), testing a sandwich immunoassay for ProADM and copeptin, and time-resolved amplified cryptate emission assay for PCT.[92] The study concluded that these three blood markers would allow for early risk stratification of individual patients at the time of emergency department admission, with ProADM being the best biomarker for mortality prediction. A more recent example of proteomic use was the development of a proteomic classifier

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88 Anuli C. Uzozie and Ruedi Aebersold, "Advancing Translational Research and Precision Medicine with Targeted Proteomics," *Journal of Proteomics* 189 (2018), https://www.sciencedirect.com/science/article/pii/S1874391918300769.

89 Irene van den Broek et al., "Automated Multiplex LC-MS/MS Assay for Quantifying Serum Apolipoproteins a-I, B, C-I, C-II, C-III, and E with Qualitative Apolipoprotein E Phenotyping," *Clinical Chemistry* 62, no. 1 (2016), https://doi.org/10.1373/clinchem.2015.246702.

90 Jennifer E. van Eyk and Michael P. Snyder, "Precision Medicine: Role of Proteomics in Changing Clinical Management and Care," *Journal of Proteome Research* 18, no. 1 (2019), https://doi.org/10.1021/acs.jproteome.8b00504.

91 Philipp Schuetz et al., "Biomarkers from Distinct Biological Pathways Improve Early Risk Stratification in Medical Emergency Patients: The Multinational, Prospective, Observational TRIAGE Study," *Critical Care* 19, no. 1 (2015), https://ccforum.biomedcentral.com/articles/10.1186/s13054-015-1098-z.

92 Schuetz et al., "Biomarkers from Distinct Biological Pathways Improve Early Risk Stratification in Medical Emergency Patients: The Multinational, Prospective, Observational TRIAGE Study."

for COVID-19 infection, using 27 biomarkers differentially expressed during infection.[93] These biomarkers included complement factors, inflammatory indicators, coagulation factors, and interleukin-6, which could help assess the severity of disease. Similarly, another study identified a protein panel which could be used to predict mortality of patients in intensive care.[94] The study used clinical data including the measurements of 321 plasma proteins, and after analysis ended up with a 14-protein panel which achieved accurate prediction of mortality. The methodologies used in the aforementioned studies could be used to develop routine proteomic assays to help in clinical-decision making, based off of predicted patient progression.

Until now, mass spectrometry-based technologies have been the standard for analyses of the proteome, including steady states and changes during various biological processes. Four types of mass analyzers are commonly used for proteomics research: quadrupole, ion trap, time-of-flight, and Fourier-transform ion cyclotron resonance.[95] Table 3 describes some advances in proteomics technology.

Table 3. Advances in Proteomic Technologies

Method	Description	Advantages	Example Uses
Ion Mobility Mass Spectrometry[96]	Separates ions in gas phase based on differences in size, shape, and charge	Allows for an additional level of protein/peptide separation, high specificity	Gas chromatography ion mobility mass spectrometry was determined to be a feasible point-of-care test to diagnose COVID-19 via breath analyses, distinguishing the disease from other respiratory conditions.[97]

[93] Christoph B. Messner et al., "Ultra-High-Throughput Clinical Proteomics Reveals Classifiers of COVID-19 Infection," *Cell Systems* 11, no. 1 (2020), https://pubmed.ncbi.nlm.nih.gov/32619549/.

[94] Vadim Demichev et al., "A Proteomic Survival Predictor for COVID-19 Patients in Intensive Care," *PLOS Digital Health* 1, no. 1 (2022), https://journals.plos.org/digitalhealth/article?id=10.1371/journal.pdig.0000007.

[95] Edouard C. Nice, "The Status of Proteomics as We Enter the 2020s: Towards Personalised/precision Medicine," *Analytical Biochemistry* 644 (2022), https://www.sciencedirect.com/science/article/pii/S0003269720303729.

[96] James N. Dodds and Erin S. Baker, "Ion Mobility Spectrometry: Fundamental Concepts, Instrumentation, Applications, and the Road Ahead," *Journal of The American Society for Mass Spectrometry* 30, no. 11 (2019), https://doi.org/10.1007/s13361-019-02288-2.

[97] Dorota M. Ruszkiewicz et al., "Diagnosis of COVID-19 by Analysis of Breath with Gas Chromatography-Ion Mobility Spectrometry - A Feasibility Study," *EClinicalMedicine* 29 (2020), https://doi.org/10.1016/j.eclinm.2020.100609.

MALDI mass spectrometry imaging[98]	Thinly sliced tissues are coated with a MALDI matrix, with a directed laser revealing spatial distributions of molecules	Absolute quantitation possible, multiple compounds detected simultaneously without labelling	MALDI MS could differentiate protein isoforms associated with patient survival in high-grade sarcomas.[99]
Top-down proteomics[100]	Intact proteins at the proteoform level are analyzed, implementing Fourier transform ion cyclotron resonance technologies	Information such as protein location, post-translational modifications can be extracted, proteins can be observed without chemical digestion	This technology has been clinically used to diagnose hemoglobinopathies and B-thalassemia.[101]
Mass cytometry[102]	Fluorescence activated cell sorting is combined with mass spectrometry, allowing for single cell analyses	High resolution analyses possible, 50 targets can be measured simultaneously per cell	Mass cytometry could differentiate between systemic sclerosis, systemic lupus erythematosus, and primary Sjogren's syndrome by characterizing immune system pathways.[103]

Another significant advance in the field of proteomics is the development of real-time protein sequencing, which is analogous to nucleotide sequencing for genomics / transcriptomics. Up until now, mass spectrometry, enzyme-linked immunosorbent assays (ELISA), and Edman degradation-based technologies have been the standard for protein sequencing/identification.[104] Edman degradation was the first method to determine the amino acid sequence of a purified peptide, in

[98] Sandra Schulz et al., "Advanced MALDI Mass Spectrometry Imaging in Pharmaceutical Research and Drug Development," *Current Opinion in Biotechnology* 55 (2019), https://doi.org/10.1016/j.copbio.2018.08.003.

[99] Sha Lou et al., "High-Grade Sarcoma Diagnosis and Prognosis: Biomarker Discovery by Mass Spectrometry Imaging," *Proteomics* 16, 11-12 (2016), https://doi.org/10.1002/pmic.201500514.

[100] Timothy K. Toby, Luca Fornelli, and Neil L. Kelleher, "Progress in Top-down Proteomics and the Analysis of Proteoforms," *Annual Review of Analytical Chemistry* 9, no. 1 (2016), https://doi.org/10.1146/annurev-anchem-071015-041550.

[101] Lidong He et al., "Diagnosis of Hemoglobinopathy and B-Thalassemia by 21 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometry and Tandem Mass Spectrometry of Hemoglobin from Blood," *Clinical Chemistry* 65, no. 8 (2019), https://doi.org/10.1373/clinchem.2018.295766.

[102] Matthew H. Spitzer and Garry P. Nolan, "Mass Cytometry: Single Cells, Many Features," *Cell* 165, no. 4 (2016), https://doi.org/10.1016/j.cell.2016.04.019.

[103] Maarten van der Kroef et al., "Cytometry by Time of Flight Identifies Distinct Signatures in Patients with Systemic Sclerosis, Systemic Lupus Erythematosus and Sjögrens Syndrome," *European Journal of Immunology* 50, no. 1 (2020), https://onlinelibrary.wiley.com/doi/full/10.1002/eji.201948129.

[104] Javier A. Alfaro et al., "The Emerging Landscape of Single-Molecule Protein Sequencing Technologies," *Nature Methods* 18, no. 6 (2021), https://www.nature.com/articles/s41592-021-01143-1#Sec4.

which the protein of interest is sequentially cleaved from the N-terminal, to identify the released amino acids by converting them to their phenylthiohydantoin derivatives. Advancements in the technology have led to techniques such as massively parallel fluorosequencing, in which Edman chemistry is combined with fluorophore chemistry and millions of fluorescently labeled peptides can be visualized in parallel.[105]

Recent novel approaches have strayed from Edman chemistry, including a significant recent breakthrough which uses an integrated semiconductor optical chip for single-molecule sequencing.[106] The study by Reed et al. described a technique where labeled proteins initially recognize the N terminus of an immobilized peptide, and the labeled proteins along with proteases allow for measurements of fluorescence intensity and binding kinetics to identify each amino acid in the sequence. This technique is poised to offer a sensitive, scalable, and accessible platform for single-molecule protein studies.

Advances in proteomics now allow for single-cell proteomics (i.e., detecting and quantifying protein levels in individual cells). A number of companies are developing instrumentation for single-cell proteomics, with examples being NanoString Technologies' GeoMx, Akoya Biosciences' CODEX, CanopyBiosciences' ChipCytometry, and Mission Bio's Tapestri. These single-cell methods can allow for high-throughput screening of samples with added data such as identification of regulatory network stages in various cell types.

In turn, this can allow for identification of therapeutic strategies based on the disease pathology.[107] An example is the single-cell IsoCode chip, which is a multiplexed chip with an antibody barcode array, which can simultaneously detect 40 secreted proteins from individual cells.[108] This chip is used to predict clinical response and toxicities of chimeric antigen receptor (CAR) therapy products by patients, allowing for evidence-based decisions to be made when selecting therapies.

Advances in protein microfabrication and microfluidics have allowed for the development of protein microarrays, which have entered the market and can detect large portions of the proteome, (e.g., Snapshot Proteomics microarray by AVMBiomed).[109] Sandwich-based antibody arrays also exist, such as RayBio's Human Cytokine Array G-series, which is used for serum analyses in

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[105] Jagannath Swaminathan et al., "Highly Parallel Single-Molecule Identification of Proteins in Zeptomole-Scale Mixtures," *Nature Biotechnology* 36, no. 11 (2018), https://www.nature.com/articles/nbt.4278.

[106] Brian D. Reed et al., "Real-Time Dynamic Single-Molecule Protein Sequencing on an Integrated Semiconductor Device," *Science* 378, no. 6616 (2022), https://doi.org/10.1126/science.abo7651.

[107] James H. Park et al., "A Single-Cell Based Precision Medicine Approach Using Glioblastoma Patient-Specific Models," *npj Precision Oncology* 6, no. 1 (2022), https://www.nature.com/articles/s41698-022-00294-4#.

[108] Carlota Arias-Hidalgo et al., "Single-Cell Proteomics: The Critical Role of Nanotechnology," *International Journal of Molecular Sciences* 23, no. 12 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9224324/.

[109] "Overview — AVMBioMed," AVMBioMed Website, accessed November 11, 2022, https://www.avmbiomed.com/services.

endometriosis patients.[110] Aptamers can bind to proteins with great specificity and affinity, and the company Somalogic has used this concept to generate reagents (SOMAmers) that improve capture, with recent studies performed by the company using their technology validating protein-phenotype models for various health indicators.[111] Similar approaches have been employed to use the proteome to characterize heart failure in a population.[112]

d. Microbiome

The human microbiome is "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space."[113] These microorganisms exist throughout the body, and perform many functions and can impact various organ systems, including the nervous system, the immune system, and the endocrine system, as well as impacting disease outcomes.[114]

This unique and commensal community creates the opportunity to establish a microbiome genetic "fingerprint" using PCR amplicon sequencing or whole genome comparison; this strategy may establish a baseline fingerprint that can be used as a comparison for future monitoring. These fingerprints may be useful not only in individual care and treatment, but may be a useful epidemiological tool to more quickly identify and control disease outbreaks.[115]

There is great potential for the microbiome to provide biomarkers for characterizing disease, identifying a prognosis, and optimizing treatment.[116] A large body of research focusing on discovering and leveraging microbiome biomarkers exists, though it largely focuses on diseases and conditions other than infectious diseases. Most research focuses on gastrointestinal diseases (such as Crohn's disease and irritable bowel syndrome),[117,118] metabolic disorders,[119] respiratory

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[110] Bao Weisheng et al., "Discovering Endometriosis Biomarkers with Multiplex Cytokine Arrays," *Clinical Proteomics* 16 (2019), https://doi.org/10.1186/s12014-019-9248-y.

[111] Stephen A. Williams et al., "Plasma Protein Patterns as Comprehensive Indicators of Health," *Nature Medicine* 25, no. 12 (2019), https://www.nature.com/articles/s41591-019-0665-2.

[112] Anna Egerstedt et al., "Profiling of the Plasma Proteome Across Different Stages of Human Heart Failure," *Nature Communications* 10, no. 1 (2019), https://www.nature.com/articles/s41467-019-13306-y.

[113] Kuntz and Gilbert, "Introducing the Microbiome into Precision Medicine," 81.

[114] Ibid, 82.

[115] Purna C. Kashyap et al., "Microbiome at the Frontier of Personalized Medicine," *Mayo Clinic Proceedings* 92, no. 12 (2017): 1857, https://doi.org/10.1016/j.mayocp.2017.10.004.

[116] Ibid.

[117] Leah B. Kosyakovsky, "The Emerging Role of the Microbiome in Precision Medicine: An Overview," *UBCMJ* 9, no. 1 (2017): 11, https://med-fom-ubcmj.sites.olt.ubc.ca/files/2017/08/Kosyakovsky-PROOF.pdf.

[118] Kashyap et al., "Microbiome at the Frontier of Personalized Medicine," 1858.

[119] Christopher Bradburne and Ada Hamosh, "Integrating the Microbiome into Precision Medicine," *Expert Review of Precision Medicine and Drug Development* 1, no. 6 (2016): 475, https://doi.org/10.1080/23808993.2016.1259562.

diseases (such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis),[120] and cancers.[121,122,123] In addition, certain gut microbiome biomarkers have been tested for diabetes, colorectal cancer, and cirrhosis.[124] Table 4 provides an overview of the field of research.

Table 4. Overview of the Body of Clinical Research on Microbiome Biomarkers

No. of Microbiome Studies on clinicaltrials.gov (as of Oct. 25, 2020)	Total Number	Completed	Ongoing	Terminated/Withdrawn/ Suspended
Therapeutics	1023	285	499	51
Diagnostics	370	72	198	16
Sensors/biosensors	16	4	12	0

Source: Derived from Celia Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices," *Advanced Materials* 33, no. 18 (2021), https://doi.org/10.1002/adma.202006104.

The gut microbiome is the focus of a large body of research due to its sheer size, complexity, and impact on the body. For example, the gut microbiome is involved in metabolism and can affect the means by which therapeutic drugs are metabolized, as well as the duration and form of their bioavailability;[125] this is especially impactful for low solubility and low permeability compounds.[126] Some drugs are inactivated by the gut microbiome and therefore made less

[120] Geraint B. Rogers and Steve Wesselingh, "Precision Respiratory Medicine and the Microbiome," *The Lancet Respiratory Medicine* 4, no. 1 (2016): 73–77, https://doi.org/10.1016/S2213-2600(15)00476-2.

[121] Laurence Zitvogel et al., "The Microbiome in Cancer Immunotherapy: Diagnostic Tools and Therapeutic Strategies," *Science* 359, no. 6382 (2018): 1366–70, https://doi.org/10.1126/science.aar6918.

[122] Han Zhang and Litao Sun, "When Human Cells Meet Bacteria: Precision Medicine for Cancers Using the Microbiota," *American Journal of Cancer Research* 8, no. 7 (2018): 1157–75, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6079160/.

[123] Tsuyoshi Hamada et al., "Integration of Microbiology, Molecular Pathology, and Epidemiology: A New Paradigm to Explore the Pathogenesis of Microbiome-driven Neoplasms," *The Journal of Pathology* 247, no. 5 (2019): 615–28, https://doi.org/10.1002/path.5236.

[124] Celia Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices," *Advanced Materials* 33, no. 18 (2021): 3–5, https://doi.org/10.1002/adma.202006104.

[125] Wuwen Feng et al., "Targeting Gut Microbiota for Precision Medicine: Focusing on the Efficacy and Toxicity of Drugs," *Theranostics* 10, no. 24 (2020): 11279, 11281, https://doi.org/10.7150/thno.47289.

[126] Kuntz and Gilbert, "Introducing the Microbiome into Precision Medicine," 84.

effective, while other therapeutics are activated and can cause cytotoxicity, such as non-steroidal anti-inflammatory drugs.[127,128]

Understanding the gut microbiome and its effects on metabolism may provide biomarker opportunities for predicting the efficacy of a given therapeutic. However, not all potentially useful biomarkers may be easy to detect; solutions such as using engineered bacteria as surrogate biomarkers to amplify the signal may help overcome this challenge.[129] In addition, establishing direct associations between the microbiome and a particular disease can be complicated due to its dynamic and individualistic nature. For a microbiome biomarker to be clinically relevant, factors such as its prevalence in the population and the impact of external factors (such as nutrition, lifestyle, and geography) must be considered and established. Gathering the data to establish these connections to a disease requires intensive longitudinal sampling and analysis.[130,131]

There are currently two primary approaches to the use of microbiome data in precision medicine: 16S rRNA sequencing and shotgun metagenomics.[132,133,134] 16S rRNA sequencing uses a target gene that contains both highly conserved (and therefore bacterially non-specific) and hypervariable (allowing for species-level identification) regions. These qualities make it a good target for bacterial identification and classification, which can provide additional detail about the bacterial strain.[135] 16S rRNA sequencing is useful for preliminary screening in determining the composition, or the "who's there" of a microbial community,[136] even if using a small sample

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[127] Kathy N. Lam, Margaret Alexander, and Peter J. Turnbaugh, "Precision Medicine Goes Microscopic: Engineering the Microbiome to Improve Drug Outcomes," *Cell Host & Microbe* 26, no. 1 (2019): 26–27, https://www.sciencedirect.com/science/article/pii/S1931312819303002?via%3Dihub.

[128] Niv Zmora et al., "Taking It Personally: Personalized Utilization of the Human Microbiome in Health and Disease," *Cell Host & Microbe* 19, no. 1 (2016): 15, https://doi.org/10.1016/j.chom.2015.12.016.

[129] Feng et al., "Targeting Gut Microbiota for Precision Medicine: Focusing on the Efficacy and Toxicity of Drugs," 11279, 11286-87, 11294-95.

[130] Joseph F. Petrosino, "The Microbiome in Precision Medicine: The Way Forward," *Genome Medicine* 10, no. 1 (2018): 2, https://doi.org/10.1186/s13073-018-0525-6.

[131] Zmora et al., "Taking it Personally: Personalized Utilization of the Human Microbiome in Health and Disease," 14.

[132] Kuntz and Gilbert, "Introducing the Microbiome into Precision Medicine," 82–83.

[133] Ava Behrouzi, Amir H. Nafari, and Seyed D. Siadat, "The Significance of Microbiome in Personalized Medicine," *Clinical and Translational Medicine* 8, no. 1 (2019): 5, https://doi.org/10.1186/s40169-019-0232-y.

[134] Gregory L. Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," *The Journal of Infectious Diseases* 223, 12 Suppl 2 (2021): S270-73, https://doi.org/10.1093/infdis/jiaa689.

[135] Kuntz and Gilbert, "Introducing the Microbiome into Precision Medicine."

[136] Mingyue Cheng, Le Cao, and Kang Ning, "Microbiome Big-Data Mining and Applications Using Single-Cell Technologies and Metagenomics Approaches Toward Precision Medicine," *Frontiers in Genetics* 10 (2019): 2, https://doi.org/10.3389/fgene.2019.00972.

size.[137] 16S rRNA sequencing requires standard next-generation sequencing equipment, which may limit its availability for use at far-forward medical treatment facilities (MTFs), but it can be useful in identifying organisms that are difficult or impossible to culture.[138]

Shotgun metagenomics typically provides a more complete microbiome genetic analysis because it sequences all genetic material in a given sample,[139] and is useful for characterizing a patient's microbiota and identifying resistance genes and microbial interactions.[140] This method is also good for determining the protein functionality, or the "what are they doing," of a microbial community such as the microbiome.[141] Computational tools can be used in conjunction with shotgun metagenomics to reconstruct sequenced fragments (if intact genetic material is not available) and identify patterns, which may be desirable for specific biomarker identification.[142] This method typically requires more complex downstream analysis and greater sequence coverage; however, shotgun metagenomics can provide more accurate species identification.[143]

Both 16S rRNA sequencing and shotgun metagenomics are generally considered to be "compositional rather than quantitative."[144] Metagenomics can provide robust identification and characterization of an infection, for example, but cannot provide the extent or potential severity of the infection. Shotgun metagenomic sequencing may be overtaking 16S rRNA sequencing as the primary method for microbiome analysis, as it tends to provide more accurate identification and more additional information due to its more thorough sequencing of all available genetic material.[145] Establishing microbiome biomarkers may help identify pathogenic respiratory microbes that may be difficult to culture or detect with other methods, as well as their susceptibility to various antibiotics.[146]

However, these are not the only available methods. Single cell sequencing uses a non-PCR method of multiple displacement amplification, which allows for high-quality genomic sequencing

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[137] Behrouzi, Nafari, and Siadat, "The Significance of Microbiome in Personalized Medicine," 5.

[138] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S272.

[139] Ibid.

[140] Kuntz and Gilbert, "Introducing the Microbiome into Precision Medicine," 82.

[141] Cheng, Cao, and Ning, "Microbiome Big-Data Mining and Applications Using Single-Cell Technologies and Metagenomics Approaches Toward Precision Medicine."

[142] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S272.

[143] Behrouzi, Nafari, and Siadat, "The Significance of Microbiome in Personalized Medicine," 5.

[144] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S273.

[145] Rogers and Wesselingh, "Precision Respiratory Medicine and the Microbiome," 78.

[146] Rogers and Wesselingh, "Precision Respiratory Medicine and the Microbiome."

of low-abundance species; however, sorting the cells from the samples can be time-consuming.[147] Quantitative polymerase chain reaction (qPCR) is a method considered to be a clinical standard of care for pathogen detection, and has shown good sensitivity over culture methods. It can define the taxonomy and antibiotic resistance of a target, though it is limited to known, pre-identified targets.[148] Other options include lateral flow assays (including the use of gold nanoparticles and quantum dots), electrochemical sensors, and plasmonic sensors such as ELISA and SPR.[149] Table 5 provides an overview of the advantages and disadvantages of a few of the primary techniques for analyzing the microbiome.

Table 5. Advantages and Disadvantages of Select Microbiome Analytical Methods

Method	Advantages	Disadvantages	Potential Solutions
16S rRNA Sequencing	Low cost Can provide taxonomic information on uncultured microbial communities	Low resolution at strain or species level Little to no functional microbial community data	Combine with metagenomics Use the software tool PICRUSt to add metagenomic and functional data
Shotgun Metagenomics	Can provide taxonomic and functional information on uncultured microbial communities Can provide full genomic data on microbes	Lack of high genome coverage Cannot associate individual phylogeny with functional genes	Combine with long-read sequencing and advanced algorithms Combine with single cell sequencing
Single Cell Sequencing	Can provide taxonomic and functional information on uncultured individual microbes Can provide high quality genomic data for low concentrations of microbes	Challenges in cell sorting Easily contaminated by other/background DNA Uneven read coverage or chimeric reads	Combine with metagenomics

Source: Derived from Mingyue Cheng, Le Cao, and Kang Ning, "Microbiome Big-Data Mining and Applications Using Single-Cell Technologies and Metagenomics Approaches Toward Precision Medicine," *Frontiers in Genetics* (2019): 2, https://doi.org/10.3389/fgene.2019.00972.

[147] Cheng, Cao, and Ning, "Microbiome Big-Data Mining and Applications Using Single-Cell Technologies and Metagenomics Approaches Toward Precision Medicine," 2–3.

[148] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S271-72.

[149] Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices," 7–10.

As an example of how microbiome analysis can aid medical diagnosis, extracellular vesicles are often used by microbes for cell-to-cell signaling, but may also cause immunogenic effects in their host (e.g., *S. aureus* extracellular vesicles trigger multiple interleukins and immunoglobulins). These extracellular vesicles harbor 16S rDNA that can be recovered from a liquid/fluid biopsy sample, such as from a lung lavage, for analysis; in addition to the 16S rDNA, antibodies against extracellular vesicles can also serve as a good biomarker for infection.[150]

Table 6 summarizes the scenarios in which different analytical methods may be used and the type of information they can provide.

Table 6. Analytical Methods and Potential Uses

Method	Bacteria	Viruses	Relative Abundance	Absolute Abundance	Species Richness	Resistome
16S rRNA Sequencing	All targets	No	Yes	No	Yes	Potentially inferred from taxonomy
Metagenomic Sequencing	Yes	Yes	Yes	No	Yes	Known resistance sequences
qPCR	Known targets	Known targets	Limited	Limited	Limited	Known resistance sequences
Culture	Culturable targets	Culturable targets	Culturable targets	Semi-quantitative in culturable targets	Culturable targets	*In vitro* phenotypic susceptibility
Quantitative Microbiome Profiling	Yes	Depends on technique	Yes	Yes	Yes	Depends on technique

Source: Derived from Gregory L. Damhorst, Max W. Adelman, Michael H. Woodworth, Colleen S. Kraft, "Current Capabilities of Gut Microbiome–Based Diagnostics and the Promise of Clinical Application," *The Journal of Infectious Diseases* 223, no. S3 (2021): S271, https://doi.org/10.1093/infdis/jiaa689.

The concept of harnessing the microbiome for diagnostics, therapeutics, and other clinical uses is still relatively new, but it is a promising area of research and development. Fuentes-Chust et al. estimate that the "microbiome therapeutics & diagnostics market is expected to grow from $506 million in 2022 to $899 million by 2025…diagnostics are expected to grow the most, due mainly to the discovery of microbiome-related biomarkers for oncology."[151]

[150] Jinho Yang et al., "A New Horizon of Precision Medicine: Combination of the Microbiome and Extracellular Vesicles," *Experimental & Molecular Medicine* 54, no. 4 (2022): 468-70, 473, https://doi.org/10.1038/s12276-022-00748-6.

[151] Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices," 4.

The DOD has shown interest in supporting microbiome research: the Army Center for Environmental Health Research is examining environmental exposure monitoring and surveillance tools, the Walter Reed Army Institute of Research is working to establish baseline upper respiratory microbiome profiles to track occupational exposures, the Air Force Research Lab is pursuing lung microbiome biomarker identification for airborne particle exposure, and the National Institutes of Health is investigating point-of-care wound diagnostics for precision antibiotic decisions.[152]

Despite the plethora of research, clinically relevant and useful microbiome diagnostic tools are still plagued by early-phase challenges. Well-defined profiling or diagnostic data is currently available for only a few diseases, and using these biomarkers to quantify an infection is still difficult.[153] More robust data is needed to establish the healthy "baseline" that enables microbiome biomarker monitoring to be a useful diagnostic; this may include clinical trials and validation, regular doctor visits (at the individual level) and population screening (to establish prevalence), and combining microbiome data with other genetic and clinical data.[154,155] Microbiome profiling and monitoring may be useful in defining disease risk stratification within a population, but more research is needed, especially in establishing the associations between specific biomarkers and a given disease[156] and over the course of a disease's progression.[157]

The microbiome presents many opportunities for biomarker identification unique to a specific pathogen, but it also provides the opportunity to assess the risk for certain pathogens based on the baseline state of the microbiome. Understanding an individual's susceptibility to certain disease exposures based on the composition of their microbiome may help prevent disease.[158] This preventative microbiome profiling analysis can both assess risk and guide future therapy decisions.[159]

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[152] Sarah Glaven et al., "The Current and Future State of Department of Defense (DoD) Microbiome Research: A Summary of the Inaugural DoD Tri-Service Microbiome Consortium Informational Meeting," *mSystems* 3, no. 4 (2018): 3, https://doi.org/10.1128/mSystems.00086-18.

[153] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S270.

[154] Petrosino, "The Microbiome in Precision Medicine: The Way Forward," 3.

[155] Damhorst et al., "Current Capabilities of Gut Microbiome-Based Diagnostics and the Promise of Clinical Application," S274.

[156] Zmora et al., "Taking it Personally: Personalized Utilization of the Human Microbiome in Health and Disease," 14.

[157] Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices," 5.

[158] Rogers and Wesselingh, "Precision Respiratory Medicine and the Microbiome."

[159] Kosyakovsky, "The Emerging Role of the Microbiome in Precision Medicine: An Overview," 11–12.

e. Metabolome

Metabolomics is "broadly defined as the comprehensive measurement of all metabolites and low-molecular-weight molecules in a biological specimen."[160] Most research on metabolomics primarily focuses on metabolic dysfunction and chronic pulmonary disease (often associated with disease severity),[161] cancer,[162,163] traumatic brain injuries, trauma, and burns,[164] COVID-19,[165] obesity, diabetes, and gastrointestinal conditions.[166]

A metabolomic profile, along with clinical and genomic data, may help identify disease variants such as COVID-19 variants.[167] Metabolomics can provide tissue-specific and time-specific data, and may help provide a more rapid approach to biomarker discovery.[168] Many sample types may be used for metabolomic analysis, including blood, urine, saliva, breath condensate, cerebrospinal fluid,[169] and synovial fluid.[170] Blood and urine are the most common sample types, as they are easy to collect and prepare.[171] Blood is less impacted by time course in the metabolite profile, but it mostly contains extracellular metabolites and therefore may not be

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[160] Clary B. Clish, "Metabolomics: An Emerging but Powerful Tool for Precision Medicine," *Cold Spring Harbor Molecular Case Studies* 1, no. 1 (2015): 1, https://doi.org/10.1101/mcs.a000588.

[161] Zeeshan Ahmed et al., "Integrative Clinical, Genomics and Metabolomics Data Analysis for Mainstream Precision Medicine to Investigate COVID-19," *BMJ Innovations* 7, no. 1 (2021): 8, https://doi.org/10.1136/bmjinnov-2020-000444.

[162] Alejandra V. Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," *Frontiers in Physiology* 7 (2016): 1–23, https://doi.org/10.3389/fphys.2016.00606 .

[163] Isabelle Kohler et al., "Integrating Clinical Metabolomics-Based Biomarker Discovery and Clinical Pharmacology to Enable Precision Medicine," *European Journal of Pharmaceutical Sciences* 109S (2017): S15, https://doi.org/10.1016/j.ejps.2017.05.018.

[164] Sudha P. Jayaraman et al., "Metabolomics and Precision Medicine in Trauma: The State of the Field," *Shock* 50, no. 1 (2018): 5–13, https://doi.org/10.1097/SHK.0000000000001093.

[165] André F. Rendeiro et al., "Metabolic and Immune Markers for Precise Monitoring of COVID-19 Severity and Treatment," *Frontiers in Immunology* 12 (2021): 1–13, https://doi.org/10.3389/fimmu.2021.809937.

[166] Vanessa Gonzalez-Covarrubias, Eduardo Martínez-Martínez, and Laura Del Bosque-Plata, "The Potential of Metabolomics in Biomedical Applications," *Metabolites* 12, no. 2 (2022): 1–32, https://doi.org/10.3390/metabo12020194.

[167] Ahmed et al., "Integrative Clinical, Genomics and Metabolomics Data Analysis for Mainstream Precision Medicine to Investigate COVID-19," 8.

[168] Clish, "Metabolomics: An Emerging but Powerful Tool for Precision Medicine," 1, 3.

[169] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 8.

[170] Xianquan Zhan, Ying Long, and Miaolong Lu, "Exploration of Variations in Proteome and Metabolome for Predictive Diagnostics and Personalized Treatment Algorithms: Innovative Approach and Examples for Potential Clinical Application," *Journal of Proteomics* 188 (2018): 35, 37. https://pubmed.ncbi.nlm.nih.gov/28851587/.

[171] Zhan, Long and Lu, "Exploration of Variations in Proteome and Metabolome for Predictive Diagnostics and Personalized Treatment Algorithms: Innovative Approach and Examples for Potential Clinical Application," 35.

the most suitable sample type for all diseases, as there may be disease-associated metabolites that are purely intracellular and are not present in the bloodstream.[172]

Dynamic biomarkers, which may change depending on certain factors, are useful for determining disease state and therapeutic response (e.g., prostate-specific antigen in cancer treatment), while static biomarkers are more useful in prognosis (e.g., gene expression or risk assessment).[173] There are many ways metabolomics may have a positive impact through the use of biomarkers, such as to better understand disease mechanisms, arrive at diagnoses and prognoses, conduct patient-specific disease state/severity binning, and to monitor therapeutic response.[174]

However, advances in metabolomics face challenges. For example, metabolites include a wide variety of potential target types, with various molecular weights, polarities, and compositions; it is estimated that there are over 19,000 different small molecule metabolites in the human body, including environmentally, dietary, and pharmacologically derived molecules.[175] In addition, changes in target metabolite levels may be very small and difficult to quantify, especially early on in the course of a disease.[176] Due to the complexity and variation of metabolites, there is currently "no single assay that can detect all metabolites present in a given sample."[177] The time sensitivity of metabolites – they are typically short-lived molecules that are easily degraded – creates the imperative to collect and process samples quickly to establish an accurate profile.[178]

Currently, a comprehensive database or understanding of the full range of the metabolome does not exist, partially due to a lack of quantitative techniques/platforms; as Xie et al. state, "the clinical usefulness and application of metabolomics has not yet been realized."[179] As such, clinical applications of metabolomics are still fairly limited.[180,181] This is partially due to the challenges in

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[172] Kohler et al., "Integrating Clinical Metabolomics-Based Biomarker Discovery and Clinical Pharmacology to Enable Precision Medicine," 517.

[173] Kohler et al., "Integrating Clinical Metabolomics-Based Biomarker Discovery and Clinical Pharmacology to Enable Precision Medicine," S15-19.

[174] Richard D. Beger et al., "Metabolomics Enables Precision Medicine: 'A White Paper, Community Perspective,'" *Metabolomics* 12, no. 10 (2016): 2, https://doi.org/10.1007/s11306-016-1094-6.

[175] Clish, "Metabolomics: An Emerging but Powerful Tool for Precision Medicine."

[176] Jens Nielsen, "Systems Biology of Metabolism: A Driver for Developing Personalized and Precision Medicine," *Cell Metabolism* 25, no. 3 (2017): 575, https://doi.org/10.1016/j.cmet.2017.02.002.

[177] Beger et al., "Metabolomics Enables Precision Medicine: 'A White Paper, Community Perspective,'" 149.

[178] Beger et al., "Metabolomics Enables Precision Medicine: 'A White Paper, Community Perspective.'"

[179] Guoxiang Xie et al., "A Metabolite Array Technology for Precision Medicine," *Analytical Chemistry* 93, no. 14 (2021): 5709, https://doi.org/10.1021/acs.analchem.0c04686.

[180] Kohler et al., "Integrating Clinical Metabolomics-Based Biomarker Discovery and Clinical Pharmacology to Enable Precision Medicine," 516.

[181] Alessandro Di Minno et al., "Challenges in Metabolomics-Based Tests, Biomarkers Revealed by Metabolomic Analysis, and the Promise of the Application of Metabolomics in Precision Medicine," *International Journal of Molecular Sciences* 23, no. 9 (2022): 4, https://doi.org/10.3390/ijms23095213.

translating research and biomarker discovery from a model system or platform to clinical use. There is also a lack of integrated platforms that can accurately and intuitively connect the "puzzle pieces" of multi-omics.[182] Finally, there is a lack of external validation for biomarker discovery research, which can lead to high false-positive rates and uncertainty in the quality of the predictive values.[183]

There are three primary study approaches in metabolomics: fingerprinting, footprinting, and profiling. Fingerprinting generally searches for metabolites within a patient,[184] but does not identify each metabolite, and associates a pattern with a given state.[185] Footprinting searches for metabolites within the patient's environment.[186] Profiling searches specifically for target metabolites in a sample.[187]

There are two primary methods of metabolomics analysis: mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy (NMR).[188] MS is very sensitive and good for the detection and quantification of a wide variety of metabolites. However, there is a need to separate metabolites by molecular weight for better sensitivity, so MS is often paired with a separation technique such as liquid chromatography (LC-MS), gas chromatography (GC-MS), or capillary electrophoresis (CE-MS).[189,190,191] GC-MS is high-resolution[192] and has good sensitivity,[193] but requires volatile reagents,[194] can involve labor-intensive sample preparation, and is not the best method for identifying new compounds.[195] LC-MS is high-sensitivity but low-resolution[196] and

[182] Nielsen, "Systems Biology of Metabolism: A Driver for Developing Personalized and Precision Medicine," 573.

[183] Nguyen P. Long et al., "Toward a Standardized Strategy of Clinical Metabolomics for the Advancement of Precision Medicine," *Metabolites* 10, no. 2 (2020): 2, https://doi.org/10.3390/metabo10020051.

[184] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

[185] Rajeev K. Azad and Vladimir Shulaev, "Metabolomics Technology and Bioinformatics for Precision Medicine," *Briefings in Bioinformatics* 20, no. 6 (2019): 1959, https://doi.org/10.1093/bib/bbx170.

[186] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

[187] Ibid.

[188] Ibid, 7–8.

[189] Ibid.

[190] Azad and Shulaev, "Metabolomics Technology and Bioinformatics for Precision Medicine," 1958–60.

[191] Jayaraman et al., "Metabolomics and Precision Medicine in Trauma: The State of the Field," 9–10.

[192] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

[193] Bingbing Li et al., "Novel Applications of Metabolomics in Personalized Medicine: A Mini-Review," *Molecules* 22, no. 7 (2017): 2, https://doi.org/10.3390/molecules22071173.

[194] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

[195] Li et al., "Novel Applications of Metabolomics in Personalized Medicine: A Mini-Review," 2.

[196] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

less robust, despite its ability to cover a wide range of metabolites.[197] CE-MS is a good technique for the simultaneous detection of a variety of targets through multiplexing.[198]

NMR allows for absolute quantification and sample preservation because it is a non-destructive method, which is useful if follow-on analysis with different techniques is desired. Some variations include H-NMR, which is the most common technique,[199] and high-resolution magic angle spinning NMR (HR-MAS-NMR),[200] which is good for liquid or intact solid tissue.[201] NMR, though somewhat limited by low sensitivity,[202,203] is an effective technique for small sample sizes.[204] It can detect metabolite concentrations of 1–2 μM in 0.5 mL, while metabolite concentrations in the nanomolar or picomolar range are typically required for early disease detection.[205]

As an example, a study on metabolome profiling for COVID-19 found that lipids might serve as good biomarkers for disease severity. Performing NMR on blood serum samples identified 168 metabolites, 56 of which had significant association ($p < 0.05$) as measured by the World Health Organization COVID-19 disease severity score. This indicates they might be a useful biomarker for disease severity. It was found that acetylated glycoproteins increased with disease severity, while low albumin concentrations indicated higher polymorphonuclear myeloid-derived suppressor cell numbers. Treatment with tocilizumab led to severe patients having a metabolite profile more similar to those with mild disease as treatment progressed.[206]

3. Clinical History

Clinical history is a broad term referring to qualitative and quantitative information about a person's health, often evaluated chronologically. This information can include data on allergies, past illnesses, surgeries, immunizations, and the results of physical exams and tests. It can also include information about medication and health habits. A family clinical history includes data on the health information of an individual's close relatives, potentially demonstrating patterns among

[197] Li et al., "Novel Applications of Metabolomics in Personalized Medicine: A Mini-Review."

[198] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 7.

[199] Azad and Shulaev, "Metabolomics Technology and Bioinformatics for Precision Medicine," 1959.

[200] Contreras et al., "Host-Microbiome Interaction and Cancer: Potential Application in Precision Medicine," 8.

[201] Azad and Shulaev, "Metabolomics Technology and Bioinformatics for Precision Medicine."

[202] Ibid, 1959.

[203] Li et al., "Novel Applications of Metabolomics in Personalized Medicine: A Mini-Review," 2.

[204] Azad and Shulaev, "Metabolomics Technology and Bioinformatics for Precision Medicine."

[205] Jayaraman et al., "Metabolomics and Precision Medicine in Trauma: The State of the Field," 6.

[206] Rendeiro et al., "Metabolic and Immune Markers for Precise Monitoring of COVID-19 Severity and Treatment," 2–5.

a family.[207] In this section, we are using the term "clinical history" to refer to datasets outside of traditional omics that can improve patient diagnosis. To discover useful insights, the breadth of clinical history requires scoping. Through our literature review, we identified four topics of relevance to clinical history, precision medicine, and diagnostics: personomics, therapeutic drug monitoring, biobanking, and image analysis.

a. Personomics

With increased emphasis on quantitative tests and decreased time for patient-physician interactions, many clinicians have been advocating for improved holistic understanding of patients. Dr. Roy Ziegelstein from Johns Hopkins School of Medicine defines personomics as the "social, psychological, cultural, behavioral and economic factors that affect the patient's health beliefs, the way he or she approaches illness, and the patient's interactions with the medical system. It considers the patient's personal preferences, his or her values and goals, and the support the patient receives from family and friends."[208]

This consideration of a patient as a person allows for improved diagnostics and clinical outcomes; Dr. Ziegelstein and his colleagues give three examples when asking a patient about their lives led to a definitive diagnosis or improved patient compliance. One such example was a patient with unexplained exacerbations of asthma that occurred around the same time each year.[209] Upon discussion, the physicians realized the woman had survived the September 11, 2001 attacks on the World Trade Center and were able to treat the underlying psychological source of her illness.[210] While some physicians obtain this information as a regular portion of their interactions with patients, it is not typically recorded and included as a part of their medical record.

The National Institute of Health and Care Excellence in the United Kingdom provides guidance on methods for learning about adult patients as individuals while obtaining their medical history.[211] This approach consists of five areas: 1) the patient as an individual, 2) the patient's life circumstances, 3) the patient's concerns, 4) the patient's needs, and 5) a reminder to clinicians to

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[207] "NCI Dictionary of Cancer Terms: Medical History," National Cancer Institute Website, accessed November 9, 2022, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/medical-history.

[208] Roy C. Ziegelstein, "Personomics and Precision Medicine," *Transactions of the American Clinical and Climatological Association* 128 (2017), https://pubmed.ncbi.nlm.nih.gov/28790500/.

[209] David B. Hellmann and Roy C. Ziegelstein, "Personomics: A New Series in the Green Journal," *The American Journal of Medicine* 130, no. 6 (2017), https://www.amjmed.com/article/S0002-9343(17)30137-7/fulltext.

[210] Hellmann and Ziegelstein, "Personomics: A New Series in the Green Journal."

[211] National Clinical Guideline Centre, *National Institute for Health and Care Excellence: Guidelines*: *CG138. Patient Experience in Adult NHS Services: Improving the Experience of Care for People Using Adult NHS Services* (London, UK: National Institute for Health Care and Excellence, 2021), https://www.ncbi.nlm.nih.gov/books/NBK11822/.

avoid making assumptions about their patients and instead ask their patients for additional information.[212]

A different report surveyed physicians who have been recognized for their clinical excellence and asked how they get to know their patients as individuals.[213] The authors identified six themes through their research: 1) the patient's concerns, 2) the patient's personal relationships, 3) the patient's hobbies and pleasurable activities, 4) open-ended questions to learn about the patient, 5) the patient's work, 6) the patient's perspective on the patient-physician relationship.[214] For military populations, information about some of these categories may already be available and could be integrated into the medical record for the purposes of personomics.

Advances in personomics are more likely to occur through training initiatives than technological innovation, though a method to incorporate these types of questions into a patient's electronic health records would still need to be developed and standardized.

b. Therapeutic Drug Monitoring

For nearly all drugs currently approved for use in humans, bioanalytical assays exist, partly because of the regulatory requirements to characterize a drug's pharmacokinetic properties during its preclinical and clinical development. However, only a few drugs are subject to routine therapeutic drug monitoring (TDM) in patients. This may be because of the lack of well-characterized relationships between serum/blood drug levels and effects, wide therapeutic windows, significant intra- and interpatient and intra and inter-occasion variability in pharmacokinetics, and cost concerns.[215]

TDM is the practice of measuring the concentration of a therapeutic agent in a patient to optimize the dosing regimen.[216] TDM may improve clinical outcomes by multiple means, including ensuring serum concentrations are kept within a drug's therapeutic windows, which can vary due to various factors such as inter-patient variation in metabolism. Physiologic variations in patients can have a great effect on drug kinetics; for example, ertapenem has a longer half-life,

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[212] National Clinical Guideline Centre, *National Institute for Health and Care Excellence: Guidelines*.

[213] Laura A. Hanyok et al., "Practicing Patient-Centered Care: The Questions Clinically Excellent Physicians Use to Get to Know Their Patients as Individuals," *Patient* 5, no. 3 (2012), https://pubmed.ncbi.nlm.nih.gov/22741807/.

[214] Ibid.

[215] Serge Cremers, Nishan Guha, and Brian Shine, "Therapeutic Drug Monitoring in the Era of Precision Medicine: Opportunities!," *British Journal of Clinical Pharmacology* 82, no. 4 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137816/.

[216] Thomas D. Pollard et al., "Electrochemical Biosensors: A Nexus for Precision Medicine," *Drug Discovery Today* 26, no. 1 (2021), https://www.sciencedirect.com/science/article/pii/S1359644620304384.

slower clearance, and higher area-under-concentration-time-curve (fAUC) in older patients compared to younger adult patients.[217]

According to WHO reports, certain criteria indicate whether a drug needs to be monitored: pharmacokinetic variability, adverse and therapeutic effects related to concentration, narrow therapeutic index, undefined range of therapeutic concentration, and difficulty in controlling desired therapeutic effect.[218] Table 7 provides examples of studies using TDM to monitor pharmaceuticals. Notably, many of these drugs are treatment options for CBRN agents (including azithromycin and vancomycin).

Table 7. Studies on TDM of Various Pharmaceuticals using Electrochemical Sensing Therapeutic Drug Monitoring

Target	Technology	Target Class	Clinical Sample Tested	Limit of Detection
Acetylcholinesterase[219]	Silver nanoparticles	Enzyme	Urine	10^{-12} M
Phenoxymethylpenicillin[220]	Microneedles	Antibiotic*	Blood/Serum	0·17 mg/L
Azithromycin[221]	Biomimetic electrochemical sensor	Antibiotic	Urine, Plasma	0.85 nM
Kanamycin[222]	Biomimetic electrochemical sensor	Antibiotic	Food	0.42 pg/ml

[217] D. G. Musson et al., "Pharmacokinetics of Total and Unbound Ertapenem in Healthy Elderly Subjects," *Antimicrobial Agents and Chemotherapy* 48, no. 2 (2004), https://doi.org/10.1128/AAC.48.2.521-524.2004.

[218] Albert Figueras Suñé, *Review of the evidence to include TDM in the essential in vitro diagnostics list and prioritization of medicines to be monitored*, (Barcelona, Spain: Catalan Foundation Institute of Pharmacology, 2019), https://cdn.who.int/media/docs/default-source/essential-medicines/2021-eml-expert-committee/other-matters/o.3_tdm-edl.pdf?sfvrsn=3e4e7953_4.

[219] Rezeda V. Shamagsumova et al., "Electrochemical Acetylcholinesterase Biosensor Based on Polylactide–Nanosilver Composite for the Determination of Anti-Dementia Drugs," *Analytical Letters* 52, no. 10 (2019), https://doi.org/10.1080/00032719.2018.1557202.

[220] Timothy M. Rawson et al., "Microneedle Biosensors for Real-Time, Minimally Invasive Drug Monitoring of Phenoxymethylpenicillin: A First-in-Human Evaluation in Healthy Volunteers," *The Lancet Digital Health* 1, no. 7 (2019), https://www.sciencedirect.com/science/article/pii/S2589750019301311.

[221] Ioan-Adrian Stoian et al., "Biomimetic Electrochemical Sensor for the Highly Selective Detection of Azithromycin in Biological Samples," *Biosensors and Bioelectronics* 155 (2020), https://www.sciencedirect.com/science/article/pii/S0956566320300956.

[222] Ibid.

Cyclophosphamide[223]	Molecularly imprinted polymer electrochemical sensor		Blood	3.4×10^{-12} mol/L
Metronidazole[224]	Molecularly imprinted polymer with carbon paste electrode sensor	Antihelminthic	Serum, Urine	9.1×10^{-8} mol/L
Ibuprofen[225]	Graphene quantum dots and gold nanoparticle	Anti-inflammatory	Serum	33.33 aM
Multiple Drugs[226]	Electrochemical aptasensor with gold nanoparticles	Antibiotics	Food	Varying (fm range)
Azithromycin[227]	Gold/graphene oxide modified carbon electrode sensor	Antibiotic	Serum	0.1 nM
Methyl paraoxon[228]	Microneedle with carbon-paste electrode sensor	Organophosphates	Skin (microneedle sensor)	20μM

[223] Bintong Huang et al., "Electrochemical Sensing Platform Based on Molecularly Imprinted Polymer Decorated N,S Co-Doped Activated Graphene for Ultrasensitive and Selective Determination of Cyclophosphamide," *Talanta* 164 (2017), https://www.sciencedirect.com/science/article/pii/S0039914016308815.

[224] Ni Xiao et al., "Carbon Paste Electrode Modified with Duplex Molecularly Imprinted Polymer Hybrid Film for Metronidazole Detection," *Biosensors and Bioelectronics* 81 (2016), https://www.sciencedirect.com/science/article/pii/S0956566316301488.

[225] Mahmoud Roushani and Faezeh Shahdost-fard, "Applicability of AuNPs@N-GQDs Nanocomposite in the Modeling of the Amplified Electrochemical Ibuprofen Aptasensing Assay by Monitoring of Riboflavin," *Bioelectrochemistry* 126 (2019), https://www.sciencedirect.com/science/article/pii/S1567539418303578.

[226] Shengfeng Huang et al., "Electrochemical Aptasensor for Multi-Antibiotics Detection Based on Endonuclease and Exonuclease Assisted Dual Recycling Amplification Strategy," *Talanta* 179 (2018), https://www.sciencedirect.com/science/article/pii/S0039914017310548.

[227] Saied Jafari et al., "An Azithromycin Electrochemical Sensor Based on an Aniline MIP Film Electropolymerized on a Gold Nano Urchins/graphene Oxide Modified Glassy Carbon Electrode," *Journal of Electroanalytical Chemistry* 829 (2018), https://www.sciencedirect.com/science/article/pii/S1572665718306544.

[228] Rupesh K. Mishra et al., "A Microneedle Biosensor for Minimally-Invasive Transdermal Detection of Nerve Agents," *Analyst* 142, no. 6 (2017), https://pubs.rsc.org/en/content/articlelanding/2017/an/c6an02625g/unauth.

An example of the advantages of TDM is seen in vancomycin, a glycopeptide antibiotic which has a narrow therapeutic range and high interpatient variability. Guidelines suggest an area under concentration-time (AUC) to minimum inhibitory concentration (MIC) ratio of >400 for clinical effectiveness.[229] High plasma concentrations also increase the likelihood of ototoxicity and nephrotoxicity; hence, drug monitoring is warranted to ensure the target concentration is reached but the chance of toxicity is not kept minimal.

A recently developed electrochemical aptamer-based sensor was designed with the target of enabling rapid convenient measurement of plasma vancomycin via finger-prick-scale samples of whole blood.[230] Tested in an animal model, this sensor allowed for closed-loop feedback control over plasma levels of the drug. Advances of such technologies could eventually lead to clinical therapeutic systems that would allow maintenance of constant plasma levels of a pharmaceutical.

The main groups of antibiotics which could benefit from TDM are aminoglycosides, glycopeptides, beta-lactams, fluoroquinolones, oxazolidinones, lipopeptides, and polymyxins.[231] Traditionally, serum measurements of antibiotics are carried out by chromatography, but newer techniques such as nanobiosensors and immunochromatography are becoming more commonplace due to various advantages, such as removed need for specialized equipment or toxic solvents.[232,233]

Herregodts et al. recently prototyped a device termed ExaBreath which could measure antibiotics in exhaled air from critically ill patients.[234] While the amounts of antibiotic quantified in exhaled air did not correlate with plasma concentration, the creators suggest alternatives such as normalization using endogenous markers to improve the correlation.[235] Table 8 provides an

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[229] Fawzy Elbarbry, "Vancomycin Dosing and Monitoring: Critical Evaluation of the Current Practice," *European Journal of Drug Metabolism and Pharmacokinetics* 43, no. 3 (2018), https://link.springer.com/article/10.1007/s13318-017-0456-4.

[230] Philippe Dauphin-Ducharme et al., "Electrochemical Aptamer-Based Sensors for Improved Therapeutic Drug Monitoring and High-Precision, Feedback-Controlled Drug Delivery," *ACS Sensors* 4, no. 10 (2019), https://doi.org/10.1021/acssensors.9b01616.

[231] Vivian Garzón, Rosa-Helena Bustos, and Daniel G. Pinacho, "Personalized Medicine for Antibiotics: The Role of Nanobiosensors in Therapeutic Drug Monitoring," *Journal of Personalized Medicine* 10, no. 4 (2020), https://doi.org/10.3390/jpm10040147.

[232] Garzón, Bustos, and Pinacho, "Personalized Medicine for Antibiotics: The Role of Nanobiosensors in Therapeutic Drug Monitoring."

[233] Nishant A. Dafale et al., "Selection of Appropriate Analytical Tools to Determine the Potency and Bioactivity of Antibiotics and Antibiotic Resistance," *Journal of Pharmaceutical Analysis* 6, no. 4 (2016), https://www.sciencedirect.com/science/article/pii/S2095177916300521.

[234] J. Herregodts et al., "Measuring Antibiotics in Exhaled Air in Critically Ill, Non-Ventilated Patients: A Feasibility and Proof of Concept Study," *Journal of Critical Care* 51 (2019), https://www.sciencedirect.com/science/article/pii/S0883944118317660.

[235] Herregodts et al., "Measuring Antibiotics in Exhaled Air in Critically Ill, Non-Ventilated Patients: A Feasibility and Proof of Concept Study."

overview of antibiotic concentration toxicities (of which many are accepted therapeutic options for CBRN agents).

Table 8. Overview of Antibiotic Toxicity and Optimal Dose

Antibiotic	Adverse Effects	Example Agent Treated with Antibiotic[236]	Dose	Maximum Concentration
Aminoglycosides				
Gentamicin	Nephrotoxicity, neurotoxicity, ototoxicity	Plague, Tularemia	5–7 mg/kg/day	5–10 mg/L
Amikacin		Plague	15–20 mg/kg/day	20–35 mg/L
Tobramycin			5–7 mg/kg/day	5–10 mg/L
Glycopeptides				
Vancomycin	Nephrotoxicity, ototoxicity, severe vesicular reactions, hemorrhagic occlusive retinal vasculitis	Anthrax	15–20 mg/kg/12 h	20–50 mg/L
Teicoplanin	Nephrotoxicity, ototoxicity, thrombocytopenia			43 mg/L
Polymyxins				
Colistin	Nephrotoxicity, Neurotoxicity		150mg (single dose)	18 µg/mL
β-Lactamics				
Penicillins				
Ampicillin-sulbactam	Thrombocytopenia, eosinophilia, leukopenia, and transient elevation of transaminases		1000:500 mg	8–37 µg/mL
Cephalosporins				
Cephalexin	Coagulation disorders, platelet function disorders, leukopenias, thrombocytopenias, neutropenias, decreased hemoglobin and hematocrit, hemolytic anemias, and nephrotoxicity		0.25 g/6 h	14 µg/mL
Cephradine			0.5–2g/6 h	12 µg/mL
Cefoxitin			1–2 g/6–8 h	20 µg/mL
Cefuroxime			0.5–1g/6–8 h	40 µg/mL
Ceftazidime		Glanders	1–2 g/8–12 h	120 µg/mL
Moxalactam			500–200 mg/kg//6–12 hr	100 µg/mL

[236] This is not an all-inclusive list, and the antibiotics listed here may be used for the treatment of more biological threat agents.

Carbapenems				
Imipenem	In high doses, neurological toxicity, seizures rarely occur. Hematological alterations, such as leukopenia, eosinophilia, or thrombocytosis, moderate and transient increases in transaminases, alkaline phosphatase. Doripenem is toxic by epidermal necrolysis and Steven-Johnson syndrome.	Anthrax	1 g	69.9 mg/L
Meropenem		Anthrax, Glanders, Melioidosis	1 g	61.6 mg/L
Ertapenem			1 g	164.6 mg/L
Doripenem		Anthrax	500 mg	23 mg/L
Quinolones				
Pipemidic acid	In some cases, tendinitis or tendon rupture. Fatal ventricular arrhythmias and neurotoxicity infrequently. Some quinolones that cause problems of phototoxicity (clinafloxacin), liver (trovafloxacin), or cardiac (grapafloxacin) toxicity have been withdrawn from the market.		400 mg	4 mg/L
Ciprofloxacin		Anthrax, Plague, Tularemia	400 mg	1.6 mg/L
Ofloxacin			400 mg	4 mg/L
Levofloxacin		Anthrax, Plague, Tularemia	500 mg	5 mg/L
Oxazolidinone				
Linezolid	Hematological toxicity, mitochondrial toxicity in blood cells and nerve fibers of the skin, hypoglycemia, lactic acidosis, and acute pancreatitis	Anthrax	1.5 mg/Kg	2.5 mg/L
Lipopeptide				
Daptomycin	Muscle toxicity. Neurological disorders (paraesthesia, dysesthesia) and eosinophilic pneumonia, skin and subcutaneous tissue disorders, hepatobiliary disorders, musculoskeletal, and connective tissue disorders.		4 mg/kg/day	62.4 µg/mL

Source: Derived from Garzón, Bustos, and Pinacho, "Personalized Medicine for Antibiotics: The Role of Nanobiosensors in Therapeutic Drug Monitoring."

ELISA techniques have also been demonstrated to successfully quantify antibiotic levels in serum, with potential use as a cost-effective and high throughput alternative to chromatographic/fluorescent methods.[237] There are several commercial kits available on the market today for quantification of antibiotics requiring TDM, such as QMS Tobramycin (Thermo

[237] Jim C. E. Odekerken et al., "ELISA-Based Detection of Gentamicin and Vancomycin in Protein-Containing Samples," *SpringerPlus* 4, no. 1 (2015), https://springerplus.springeropen.com/articles/10.1186/s40064-015-1411-y.

Fisher), QMS Gentamicin (Thermo Fisher), QMS Vancomycin (Thermo Fisher), Monoclonal Antibody Penicillin (Thermo Fisher), and the ARK Linezolid Assay (ARK Diagnostics).

Electrochemical sensors work by measuring electric potential differences (potentiometric), current generation (amperometric), or by changes in conductance (impedimetric). Aminoglycosides have been quantified in blood serum using electrochemical biosensors, using RNA aptamers that work in the therapeutic range of 2-6 micromolar.[238] The aminoglycoside sensor described has multiple attributes which would enable it to be a point-of-care diagnostic device, including reusability, compactness, speed of results, and having no reagent requirement. The creators of the sensor have outlined its ability to be implemented in a hand-held device format for ease of use. Amperometric biosensors have also been developed, an example being a kanamycin sensor using a label-free immunosensor on a water-soluble graphene sheet. The sensor was shown to have a limit of detection (LOD) of 6.3 pg/ml,[239] with traditional high-powered liquid chromatography (HPLC) having a LOD in the range of 0.01 μg/ml.[240]

Optical biosensors also have various characteristics that would make them a good candidate for TDM, including high sensitivity, portability, and reproducibility. Vancomycin has been detected in plasma by imprinted polymer nanoparticles, with a LOD of 0.0032ng/ml.[241] Optical biosensors are also commonplace in the food industry to detect antibiotics in food, with a portable optofluidic-based biosensing platform developed for sulfadimidine testing.[242]

For example, when a polarized light beam is directed to a lower refractive index later between a prism and a sample, the light generates excitation of a surface plasmon for a certain angle of incidence of the light beam, which is known as the resonance angle. Surface plasma resonance (SPR) sensors act on the principle of the displacement of the resonance angle when an analyte binds with a recognition element. Tobramycin has been detected using a portable SPR device in patient serum, with a LOD of 3.4um.[243] This sensor was palm-sized, inexpensive, and portable. A

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[238] Aaron A. Rowe, Erin A. Miller, and Kevin W. Plaxco, "Reagentless Measurement of Aminoglycoside Antibiotics in Blood Serum via an Electrochemical, Ribonucleic Acid Aptamer-Based Biosensor," *Analytical Chemistry* 82, no. 17 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3082472/.

[239] Yanfang Zhao et al., "Label-Free Electrochemical Immunosensor for Sensitive Detection of Kanamycin," *Sensors and Actuators B: Chemical* 155, no. 2 (2011), https://www.sciencedirect.com/science/article/pii/S0925400511000360.

[240] Xingping Zhang et al., "Determination of Kanamycin by High Performance Liquid Chromatography," *Molecules* 24, no. 10 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572613/.

[241] Sergiy Korposh et al., "Selective Vancomycin Detection Using Optical Fibre Long Period Gratings Functionalised with Molecularly Imprinted Polymer Nanoparticles," *Analyst* 139, no. 9 (2014), https://pubs.rsc.org/en/content/articlelanding/2014/AN/C3AN02126B.

[242] Xiu-Juan Hao et al., "Portable and Reusable Optofluidics-Based Biosensing Platform for Ultrasensitive Detection of Sulfadimidine in Dairy Products," *Sensors* 15, no. 4 (2015), https://pubmed.ncbi.nlm.nih.gov/25860072/.

[243] Giulia Cappi et al., "Label-Free Detection of Tobramycin in Serum by Transmission-Localized Surface Plasmon Resonance," *Analytical Chemistry* 87, no. 10 (2015), https://pubmed.ncbi.nlm.nih.gov/25811093/.

large number of SPR applications have been created for the detection of antibiotics in food, the methodology of which could be used for the detection of antibiotics in clinical samples such as sera.[244]

c. Biobanking

Biobanks are large collections of biological specimens linked to relevant personal and health information (e.g., health records, family history, lifestyle, omics data) that are held primarily for use in health and medical research.[245] Biobanks can be classified by a few different schemes, including the type of research (e.g., population-level studies, translational studies, or pathology archives), the type of samples collected (e.g., frozen tissues, formalin-fixed tissues, cells, whole blood, urine), the type of donor or patient (e.g., healthy donors or donors with a particular condition), collection methods and study design (e.g., retrospective or prospective accrual of samples), nature of the intended user (e.g., single group or user, institution), or whether the biobank is physical, all virtual, or a combination of the two.[246] As precision medicine technologies advance, biobanking enables researchers to return to original samples for additional analyses that were not possible when the data was originally collected.

One type of biobanking particularly relevant to precision medicine diagnostics is longitudinal biobanking, where samples are collected from a patient over time. These samples can be used for biomarker discovery and investigation. Notably, the DoD has maintained one of the largest biobanks in the world at the DoD Serum Repository, containing over 62 million longitudinal blood-derived serum samples that can be linked to deployment data, pharmaceutical data, microbiological lab test results, and electronic records.[247]

In one recent example using biobanks to understand medical outcomes, blood samples and symptom data were collected from UK Biobank participants monthly for a six-month period to determine whether COVID-19 antibodies remained in the circulation after infection.[248] They found that 99 percent of participants who tested positive for SARS-CoV-2 retained antibodies against

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[244] Garzón, Bustos, and Pinacho, "Personalized Medicine for Antibiotics: The Role of Nanobiosensors in Therapeutic Drug Monitoring."

[245] Laura Annaratone et al., "Basic Principles of Biobanking: From Biological Samples to Precision Medicine for Patients," *Virchows Archiv* 479, no. 2 (2021), https://doi.org/10.1007/s00428-021-03151-0.

[246] Annaratone et al., "Basic Principles of Biobanking: From Biological Samples to Precision Medicine for Patients."

[247] "Department of Defense Serum Repository," Military Health System Website, accessed November 29, 2022, https://health.mil/Military-Health-Topics/Health-Readiness/AFHSD/Data-Management-and-Technical-Support/Department-of-Defense-Serum-Repository.

[248] UK Biobank, "UK Biobank Study Shows That COVID-19 Antibodies Remain for at Least 6 Months Post-Infection for the Vast Majority of People Who Have Had the Virus," February 3, 2021, https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/news/uk-biobank-study-shows-that-covid-19-antibodies-remain-for-at-least-6-months.

the virus for three months and 88 percent retained antibodies for six months.[249] This type of data could indicate the need for additional intervention for those patients who did not maintain circulating antibodies.

Another type of biobanking with potential relevance for diagnostics and therapeutic development is cell or tissue banking with the purpose of developing patient-derived organoids. Organoids are "self-organizing, expanding 3D cultures derived from stem cells."[250] Patient-derived organoids can serve important purposes, particularly for cancer diagnosis and treatment options. The drug response of patient-derived organoids has been shown to correlate well with overall patient drug response, suggesting their use in companion diagnostics to determine appropriate cancer treatments. Additionally, organoids and organ-on-a-chip technologies have been suggested as research tools to develop countermeasures for radiation, and they may be useful tools in developing new diagnostics for a variety of CBRN agents.[251]

Biobanking can also be of tremendous use when developing new diagnostic tests. To research, develop, and validate new diagnostics, clinical samples need to be made available to researchers conducting those analyses, but often these samples are siloed due to physical distance, legal obstacles for sample sharing, or researchers not knowing about available collections. Even for high priority diseases such as COVID-19, obtaining samples—particularly from diverse demographics—was difficult during the beginning of the pandemic.[252] New resources such as DxConnect Virtual Biobank provide a service that connects researchers to available samples, reducing this bottleneck.[253] Currently this resource only is linked to COVID-19, but DxConnect aims to increase the represented samples to include tuberculosis, HIV, malaria, hepatitis, fever-related infections, and neglected tropical diseases in the future.[254]

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[249] Ibid.

[250] Shree Bose, Hans Clevers, and Xiling Shen, "Promises and Challenges of Organoid-Guided Precision Medicine," *Med* 2, no. 9 (2021), https://doi.org/10.1016/j.medj.2021.08.005.

[251] Gordana Vunjak-Novakovic et al., *Human Organs-on-a-Chip Platforms for Developing Countermeasures to Space Radiation: Topical White Paper*, (New York, NY: Columbia University, 2021), http://surveygizmoresponseuploads.s3.amazonaws.com/fileuploads/623127/6378869/20-3b2763af34355557c9b2552c617f9c5e_VunjakNovakovicGordanaV.pdf.

[252] Shubhagata Das and Sherry Dunbar, "The COVID-19 Pandemic - A Diagnostic Industry Perspective," *Frontiers in Cellular and Infection Microbiology* 12 (2022), https://doi.org/10.3389/fcimb.2022.862440.

[253] Stefano Ongarello, Marta Fernández Suárez, and Fay Betsou, "The DxConnect Virtual Biobank Connects Diagnostic Researchers to Clinical Samples," *Nature Biotechnology* 40, no. 1 (2022), https://doi.org/10.1038/s41587-021-01168-z.

[254] Ibid.

d. Image Analysis/Radiomics

Medical imaging has been used to diagnose patients and monitor treatment outcomes since the 1890s when x-rays were first discovered.[255] New advancements in machine learning have turned the relatively qualitative field of medical imaging into a rich source of quantitative data. Radiomics has been defined as "the rapidly evolving field of research concerned with the extraction of quantitative metrics—the so-called radiomic features—within medical images."[256] Radiomics can capture information from images such as tissue and lesion properties (e.g. size, shape, and heterogeneity). If multiple images are taken over time, information about the disease progression, treatment effectiveness, and discovery of new biomarkers can be outputs of radiomics.

Several applications of radiomics in infectious disease diagnostics have been chronicled in the academic literature. For example, groups have investigated the use of computed tomography (CT) imaging to diagnose patients with COVID-19. In one study, researchers developed a deep learning model for identification of COVID-19 infection using chest CT scans. They collected CT images from patients with COVID-19 or community acquired pneumonia from three different medical centers and determined the clinical utility of their methods.[257] They found that the deep learning models were as sensitive as senior radiologists and more efficient (5.15 vs 38 minutes from imaging until time to diagnosis), and could serve as a screening method.[258] This type of diagnostic modality would be particularly useful for uncommon infectious diseases such as some biothreat agents, where clinicians may lack familiarity and an index of suspicion.

In addition to diagnostics of infectious diseases, radiomics can be used to determine tissue damage following radiation. Another recent study involved the use of radiomics for patient diagnosis in cases of chronic kidney disease induced as a side effect of radiation therapy for cancer.[259] In this study, the CT images of 50 patients were analyzed to determine radiomic features useful in diagnosing chronic kidney disease and predicting chronic kidney radiation toxicities.[260]

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[255] James H. Scatliff and Peter J. Morris, "From Roentgen to Magnetic Resonance Imaging: The History of Medical Imaging," *North Carolina Medical Journal* 75, no. 2 (2014), https://doi.org/10.18043/ncm.75.2.111.

[256] Marius E. Mayerhoefer et al., "Introduction to Radiomics," *Journal of Nuclear Medicine* 61, no. 4 (2020), https://doi.org/10.2967/jnumed.118.222893.

[257] Xiaoguo Zhang et al., "A Deep Learning Integrated Radiomics Model for Identification of Coronavirus Disease 2019 Using Computed Tomography," *Scientific Reports* 11, no. 1 (2021), https://doi.org/10.1038/s41598-021-83237-6.

[258] Ibid.

[259] Sepideh Amiri et al., "Radiomics Analysis on CT Images for Prediction of Radiation-Induced Kidney Damage by Machine Learning Models," *Computers in Biology and Medicine* 133 (2021), https://doi.org/10.1016/j.compbiomed.2021.104409.

[260] Ibid.

While not directly related to CBRN defense, this type of analysis might be useful in the future for determining organ toxicity following acute radiation exposure.

B. Diagnostic Technologies

The development of diagnostic technologies that employ precision medicine concepts is still in its early stages. Development of host-based assays for diagnosing and establishing prognosis would most likely consider adopting the WHO's ASSURED guidelines for diagnostics in the developing world. Many characteristics of these WHO guidelines are applicable to scenarios faced by personnel in austere environments or combat situations.[261] These guidelines suggest a diagnostic should be Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free, and Delivered (ASSURED) to those who need it. The current cost and infrastructure required for host-based assays such as transcriptomic profiling is higher than other diagnostic assays currently available, but developments in point-of-care technology are moving towards low-cost, multiplexed, equipment-free systems.

An analysis of state-of-the-art diagnostic technologies has been documented in IDA Paper P-33049.[262] This document gives special consideration to diagnostic technologies that may be favorable for far-forward use, but many of the technologies considered are directly relevant to precision medicine. Some of the technologies described in the study have been highlighted below, but a more detailed analysis can be found in P-33049.

1. Nanomaterials

Nanomaterials consist of both active nanostructures (3D transistors, amplifiers, actuators), passive nanostructures (coatings, nanoparticles, nanostructured metals, etc.), and molecular nanosystems.[263] Nanomaterials have characteristics which may make them ideal portable biosensors, with the potential for ultra-sensitive detection of analytes of interest. These characteristics are primarily due to electron and phonon (i.e., the unit of vibrational energy in a

[261] David Mabey et al., "Diagnostics for the Developing World," *Nature Reviews Microbiology* 2, no. 3 (2004), https://doi.org/10.1038/nrmicro841.

[262] Catherine Scheible et al., Analysis of State-of-the-Art Diagnostics for Far-Forward Use, IDA Paper P-33049, (Alexandria, VA: Institute for Defense Analyses, July 2022).

[263] Calabretta et al., "Precision Medicine, Bioanalytics and Nanomaterials: Toward a New Generation of Personalized Portable Diagnostics."

crystal lattice[264]) confinement, high surface-to-volume ratios, high surface reaction activity, high adsorption ability, and high catalytic efficiency.[265]

An example is an immunoassay device for rapid human ferritin detection using gold nanorods as the reported probe for antibody labelling. The device is similar to a lateral flow assay, with the output being a visually detectable color change, or electrochemical detection for quantification.[266] Carbon-based nanomaterials, such as fullerenes, carbon nanotubes, and graphene area, also provide advantages due to their physical and chemical properties. Carbon nanotubes (CNTs) have been widely used as electrode materials in electrochemical biosensing, and have been clinically useful in the detection of carbohydrate antigen 19-9, a marker in cases of pancreatic cancer.[267] Multi-walled carbon nanotubes increase conductivity and active surface area of the sensing platform, as demonstrated in a tool designed to rapidly detect target DNA with a detection limit of 40pM.[268]

2. Quantum dots

Quantum dots (QDs) are inorganic semiconductor nanocrystals, with diameters in the range of 2–10 × 10^{-9} m, that display a range of unique optoelectronic properties. They have broad excitation spectra and narrow emission spectra, and their emission wavelengths can be tuned by changing the size of the nanoparticle; this creates great potential for fluorescence sensing applications. QDs have been used in multiple applications in order to improve detection limits, and decrease instrumentation requirements.[269] QD-mediated fluorescence resonance energy

[264] Lin Qiu et al., "A Review of Recent Advances in Thermophysical Properties at the Nanoscale: From Solid State to Colloids," *Physics Reports* 843 (2020), https://www.sciencedirect.com/science/article/pii/S0370157319304016.

[265] Calabretta et al., "Precision Medicine, Bioanalytics and Nanomaterials: Toward a New Generation of Personalized Portable Diagnostics."

[266] Ting-Ting Song et al., "Electrochemical Detection of Human Ferritin Based on Gold Nanorod Reporter Probe and Cotton Thread Immunoassay Device," *Chinese Chemical Letters* 28, no. 2 (2017), https://www.sciencedirect.com/science/article/pii/S1001841716302455.

[267] Xin Zhang et al., "An Ultrasensitive Multi-Walled Carbon Nanotube-Platinum-Luminol Nanocomposite-Based Electrochemiluminescence Immunosensor," *Analyst* 142, no. 12 (2017), https://pubs.rsc.org/en/content/articlelanding/2017/AN/C7AN00417F.

[268] Wanwei Qiu et al., "Carbon Nanotube-Based Lateral Flow Biosensor for Sensitive and Rapid Detection of DNA Sequence," *Biosensors and Bioelectronics* 64 (2015), https://www.sciencedirect.com/science/article/pii/S0956566314007155.

[269] Catherine Scheible et al., Analysis of State-of-the-Art Diagnostics for Far-Forward Use, IDA Paper P-33049, (Alexandria, VA: Institute for Defense Analyses, July 2022).

transfer (FRET) nanosensors have been created; these can help distinguish rare mutations (~0.001 percent) from mixtures for highly sensitive single nucleotide polymorphism (SNP) detection.[270]

3. Paper based diagnostics

Paper-based diagnostic technologies may prove essential in spreading precision medicine concepts to low-resource situations. A useful tool implementing this concept is the paper-based 10 SNP panel, which detects a genetic signature associated with breast cancer, and provides a visual output.[271] The device is a lateral flow assay in gold nanoparticles (AuNPs) functionalized with anti-biotin that were immobilized to allow capture of complimentary tag sequences. The presence of the target alleles caused red spots to form on the paper, removing the need for instrumentation for detection. The same concept could potentially be used to screen for other nucleotide sequences, potentially identifying polymorphisms of interest to classify patients based on their genetic makeup. Paper-based devices may also employ microfluidics to detect analytes such as pathogens or biomarkers like glucose, hepatitis antibodies, Ebola virus RNA, or NO_2 in saliva.[272,273,274,275]

4. Digital PCR

Digital PCR (dPCR) involves an approach of partitioning an input sample into multiple parallel PCR reactions using microfluidic processes. After amplification, each well can be measured to produce a binary readout, with the fraction of positive readouts and a Poisson distribution used to estimate the target's initial concentration in the sample.

This method is highly quantitative, does not require a reference sample, and has the potential to be more sensitive and specific than traditional PCR, with potential single molecule sensitivity. dPCR has been shown in cases to be more sensitive than NGS for testing and identification of rare

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[270] Chen-Chen Li et al., "Development of a Single Quantum Dot-Mediated FRET Nanosensor for Sensitive Detection of Single-Nucleotide Polymorphism in Cancer Cells," *Analytical Chemistry* 93, no. 43 (2021), https://pubs.acs.org/doi/10.1021/acs.analchem.1c03675.

[271] Aikaterini Galaziou, Theodore K. Christopoulos, and Penelope C. Ioannou, "Paper-Based Device Providing Visual Genetic Signatures for Precision Medicine: Application to Breast Cancer," *Analytical and Bioanalytical Chemistry* 411, no. 17 (2019), https://link.springer.com/article/10.1007/s00216-019-01838-7.

[272] Laura Magro et al., "Paper Microfluidics for Nucleic Acid Amplification Testing (NAAT) Of Infectious Diseases," *Lab on a Chip* 17, no. 14 (2017), https://doi.org/10.1039/C7LC00013H.

[273] Samir A. Bhakta et al., "Determination of Nitrite in Saliva Using Microfluidic Paper-Based Analytical Devices," *Analytica Chimica Acta* 809 (2014), https://doi.org/10.1016/j.aca.2013.11.044.

[274] Ellen Gabriel et al., "Paper-Based Colorimetric Biosensor for Tear Glucose Measurements," *Micromachines* 8, no. 4 (2017), https://doi.org/10.3390/mi8040104.

[275] Chen Zhao and Xinyu Liu, "A Portable Paper-Based Microfluidic Platform for Multiplexed Electrochemical Detection of Human Immunodeficiency Virus and Hepatitis C Virus Antibodies in Serum," *Biomicrofluidics* 10, no. 2 (2016), https://aip.scitation.org/doi/10.1063/1.4945311.

(<1 percent prevalence) mutations, and has been shown to detect 0-5 copies of genes with a small coefficient of variation (<3 percent).[276,277]

5. CRISPR

Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas-based systems take advantage of the high specificity/sensitivity of natural CRISPR systems for diagnostic purposes.[278] CRISPR is a natural defense mechanism of single-celled organisms, which identifies and cleaves specific nucleotide sequences foreign to the host cell. CRISPR systems consist of a Cas protein and a guide RNA. The guide RNA (gRNA) has the function of identifying a nucleotide sequence, which the Cas protein depends on to cleave the target sequence.

This cleavage property can be leveraged to identify target sequences with high accuracy, and by modifying the guide RNA, the CRISPR system can be used to target a nucleotide sequence of choice. Cas9, Cas12, and Cas13 are the most common proteins used along with CRISPR. Cas9 is the most well-known CRISPR system, consisting of only one Cas9 protein that has target DNA-cleaving ability. Cas 12 and Cas13, on the other hand, have collateral cleavage activity; this means that along with the target sequence, they also cleave nearby non-target sequences. Cas13 is also a ribonuclease, and therefore instead of DNA it cleaves RNA.

Various CRISPR assays have been created for nucleic acid detection. For example, CRISPR-Chip is a CRISPR-enhanced graphene-based field-effect transistor (gFET) tool which uses graphene functionalized with the dCas9 enzyme as a channel between source and drain electrodes. The binding of the target nucleotide sequence to the dCas9 complex causes electrical modulation of the gFET. This technique can be used for rapid sensitive detection of target sequences and was used to detect Duchenne muscular dystrophy-associated mutations with an LOD of 3.3ng/μL (1.7×10^{-15} M genomic material), with a sample-to-result time of 15 minutes, without the need for DNA amplification.[279]

Cas13 is an RNA-guided ribonuclease, acting through crRNA-target pairing. A Cas13a-based system termed SHERLOCK (Specific High-Sensitivity Enzymatic Reporter UnLOCKing) has

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[276] Megan E. Dueck et al., "Precision Cancer Monitoring Using a Novel, Fully Integrated, Microfluidic Array Partitioning Digital PCR Platform," *Scientific Reports* 9, no. 1 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6925289/.

[277] Deborah L. Stabley et al., "SMN1 and SMN2 Copy Numbers in Cell Lines Derived from Patients with Spinal Muscular Atrophy as Measured by Array Digital PCR," *Molecular Genetics & Genomic Medicine* 3, no. 4 (2015), https://onlinelibrary.wiley.com/doi/10.1002/mgg3.141.

[278] Xiaohong Xiang et al., "CRISPR-Cas Systems Based Molecular Diagnostic Tool for Infectious Diseases and Emerging 2019 Novel Coronavirus (COVID-19) Pneumonia," *Journal of Drug Targeting* 28, 7-8 (2020), https://doi.org/10.1080/1061186X.2020.1769637.

[279] Reza Hajian et al., "Detection of Unamplified Target Genes via CRISPR-Cas9 Immobilized on a Graphene Field-Effect Transistor," *Nature Biomedical Engineering* 3, no. 6 (2019), https://doi.org/10.1038/s41551-019-0371-x.

been shown to identify mutations in tumor DNA.[280] SHERLOCK combines reverse transcription recombinase polymerase amplification (RT-RPA) with Cas13a nuclease activity and uses a crRNA-Cas13a complex to bind to the target sequence, which in turn activates RNAse activity. This RNAse activity degrades non-target RNA, which causes fluorescence. Multiple variations of SHERLOCK have been implemented, including an FDA-approved commercial assay for SARS-CoV-2.

6. Artificial Intelligence / Machine Learning

Artificial Intelligence (AI) and Machine Learning (ML) approaches are common ways to explain large datasets and produce actionable insights. This makes these approaches directly applicable to precision medicine approaches. AI and ML are useful in analyzing metabolomic profile data and establishing disease associations, thereby supporting the concept of predictive diagnostics.[281] For instance, AI/ML platforms can identify continuous drug administration parameters for optimal dosing.[282] Combined with TDM, this could allow for a significant increase in the efficiency of administered therapeutics, tailoring concentrations for each patient while also ensuring that the target concentrations are achieved.

Google's DeepMind Health project and IBM's Watson are some of the leading programs for the implementation of AI in clinical practice.[283] IBM's Watson can recognize data in clinical notes and reports, and then provides essential oncology decision support tools for creating optimized treatment plans for patients. As described in Image Analysis/Radiomics, the field of radiogenomics focuses on establishing associations among imaging features to predict a patient's risk / clinical progression.[284] The majority of work in this field has been performed for cancer therapeutics,[285] but various methodologies applied using AI/ML technologies should be applicable to various subdomains of precision medicine.

For instance, Huang et al. developed a machine learning tool to predict individual patient responses to cancer therapeutics with a high accuracy, based on the patient's genome.[286] Similar

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[280] Jonathan S. Gootenberg et al., "Nucleic Acid Detection with CRISPR-Cas13a/C2c2," *Science* 356, no. 6336 (2017), https://doi.org/10.1126/science.aam9321.

[281] Ahmed et al., "Integrative Clinical, Genomics and Metabolomics Data Analysis for Mainstream Precision Medicine to Investigate COVID-19."

[282] Shraddha Chakradhar, "Predictable Response: Finding Optimal Drugs and Doses Using Artificial Intelligence," *Nature Medicine* 23, no. 11 (2017), https://www.nature.com/articles/nm1117-1244.

[283] Bertalan Mesko, "The Role of Artificial Intelligence in Precision Medicine," *Expert Review of Precision Medicine and Drug Development* 2, no. 5 (2017), https://doi.org/10.1080/23808993.2017.1380516.

[284] Kevin B. Johnson et al., "Precision Medicine, AI, and the Future of Personalized Health Care," *Clinical and Translational Science* 14, no. 1 (2021), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7877825/.

[285] Ibid.

[286] Cai Huang et al., "Machine Learning Predicts Individual Cancer Patient Responses to Therapeutic Drugs with High Accuracy," *Scientific Reports* 8, no. 1 (2018), https://doi.org/10.1038/s41598-018-34753-5.

tools may be developed for other classes of therapeutics for other conditions, such as the use of antibiotics in treating infections. These tools can also be combined with many other diagnostic technologies to implement precision medicine concepts. For example, MALDI-TOF Mass Spectrometry was combined with a neural network approach to create a tool that could identify methicillin resistance in *Staphylococcus aureus* clinical isolates.[287]

7. ELISA

Enzyme-linked Immunosorbent Assay (ELISA) uses antibodies to detect a given antigen or other target, by attaching these antibodies to a reporter molecule. ELISA itself is not a novel advancement and is a standard diagnostic tool for various purposes, but there have been many advancements in ELISA technologies that are relevant to precision medicine.

SiMoa (Single Molecule Assay) is an ultrasensitive ELISA-based tool which uses a bead-based sandwich immunoassay approach, sealing beads with oil to ensure only one bead is present in each well (there is one enzyme-labelled immunocomplex).[288] This allows for a low limit of detection (in the range of 10 molecules per 100µL sample). Another technology that has allowed for increased sensitivity in detecting biomarkers is graphene nanoparticle-based ELISA, in which graphene oxide sheets, which act as nanocarriers, are antibody-functionalized.[289] This technique has been tested in multiple applications, such as the detection of amyloid beta, an Alzheimer's Disease biomarker. Another technology which improves both the sensitivity and portability/accessibility of ELISA is the paper-based ELISA test (p-ELISA), with a portable p-ELISA kit designed to detect C-reactive protein, an inflammatory biomarker for multiple disease and conditions, with a low limit of detection of 1µg/ml in blood.[290]

The analysis of ELISA technologies above has been adapted from IDA Paper P-33049.[291] The paper presents in-depth analyses of multiple similar diagnostic technologies with direct relevance to precision medicine, and the study may act as an extension to this section.

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[287] M. Camoez et al., "Automated Categorization of Methicillin-Resistant Staphylococcus Aureus Clinical Isolates into Different Clonal Complexes by MALDI-TOF Mass Spectrometry," *Clinical Microbiology and Infection* 22, no. 2 (2016), https://pubmed.ncbi.nlm.nih.gov/26482268/.

[288] Danni Li and Michelle M. Mielke, "An Update on Blood-Based Markers of Alzheimer's Disease Using the SiMoA Platform," *Neurology and Therapy* 8, Suppl 2 (2019), https://link.springer.com/article/10.1007/s40120-019-00164-5.

[289] Jing Zhao et al., "Graphene Oxide-Gold Nanoparticle-Aptamer Complexed Probe for Detecting Amyloid Beta Oligomer by ELISA-Based Immunoassay," *Journal of Immunological Methods* 489 (2021), https://pubmed.ncbi.nlm.nih.gov/33333060.

[290] Mohit S. Verma et al., "Sliding-Strip Microfluidic Device Enables ELISA on Paper," *Biosensors and Bioelectronics* 99 (2018), https://www.sciencedirect.com/science/article/pii/S0956566317304815.

[291] Catherine Scheible et al., Analysis of State-of-the-Art Diagnostics for Far-Forward Use, IDA Paper P-33049, (Alexandria, VA: Institute for Defense Analyses, July 2022).

C. Agents / Diseases

The National Human Genome Research Institute and European Bioinformatics Institutes' joint database of GWAS was used to identify genome-wide associations for various biological and chemical agents. As seen in the results depicted in Table 9, associations are lacking for most agents. However, due to the SARS-CoV-2 pandemic, there has been a spur of interest in precision medicine and association studies, and multiple studies have attempted to associate COVID-19 with various markers in order to predict clinical trajectories. These methods may be directly applicable to other agents of interest in the future.

Table 9. Agent Associations Identified using the NHGRI-EBI Catalog of Genome-wide Association Studies

Agent	Number of Associations[292]	Number of studies[293]
B. anthracis	8	1
Botulinum Toxin	0	0
C. burnetii	0	0
Eastern Equine Encephalitis[294]	0	1
F. tularensis	0	0
Lassa Fever Virus	0	0
Marburg Virus	0	0
Monkeypox	0	0
Ricin	0	0
Rickettsia	0	0
1918 Influenza	0	0
SARS-CoV-2	823	131
Staphylococcal enterotoxin	0	0
T-2 toxin	0	0
Variola	130	2
Y. pestis	0	0
B. mallei	0	0
B. pseudomallei	0	1
Organophosphates	0	0
Chlorine	0	0
Influenza (General)	103	5
Enterobacteriaceae	5	1
Tuberculosis	205	19
Sepsis	47	6

[292] The total number of associations includes associations with vaccine responses.

[293] "Study" refers to an article published in a scientific journal, which is different than the GWAS Catalog's definition of "study." As per the catalog's definitions, one publication may have multiple studies.

[294] Viral encephalitis in general had one reported study, but no reported associations.

Below are highlighted precision medicine concepts relevant to a few representative biological or chemical agents. Highlighted associations may not have been present in the NHGRI-EBI database, and therefore may not be reflected in Table 9. This is not a comprehensive list of all the associations identified per agent, nor is it a comprehensive list of all agents/diseases, but the section highlights potential targets for enacting precision medicine concepts and modifying diagnostic technologies accordingly.

The descriptions of the agents also serve as an introduction to the various methodologies available for implementing precision medicine concepts, while highlighting biomarkers, genetic variations, and other targets that can be detected with the use of diagnostic technologies.

1. Anthrax

Various association studies have been performed to identify factors related to anthrax susceptibility. Expression levels of anthrax toxin receptor 2 (ANTXR2) are strongly correlated with anthrax toxin susceptibility. Gene loci containing regulatory elements of ANTXR2 were identified, including regulatory SNPs (rs13140055 and rs80314910) which may cause variability in expression and hence account for interindividual toxin susceptibility variation.[295] Human studies regarding the transcriptome also have shown associations with toxin susceptibility, with sensitivity to the PA moiety of the anthrax toxin being correlated to CMG2 RNA abundance in cells.[296]

Animal models have also shown significant results in this domain. Multiple genes, including the Kif1C[297] and Nalp1b[298] gene, along with quantitative trait loci[299] have all been shown to have associations with anthrax toxin susceptibility. While not tested in humans, these regions do have human analogues, laying out direction for future studies.

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[295] Zhang et al., "Anthrax Susceptibility: Human Genetic Polymorphisms Modulating ANTXR2 Expression," *Toxins* 8, no. 1 (2015), https://doi.org/10.3390/toxins8010001.

[296] Mikhail Martchenko et al., "Human Genetic Variation Altering Anthrax Toxin Sensitivity," *Proceedings of the National Academy of Sciences of the United States of America* 109, no. 8 (2012), https://doi.org/10.1073/pnas.1121006109.

[297] James W. Watters et al., "Kif1C, a Kinesin-Like Motor Protein, Mediates Mouse Macrophage Resistance to Anthrax Lethal Factor," *Current Biology* 11, no. 19 (2001), https://www.cell.com/fulltext/S0960-9822(01)00476-6.

[298] Eric D. Boyden and William F. Dietrich, "Nalp1b Controls Mouse Macrophage Susceptibility to Anthrax Lethal Toxin," *Nature Genetics* 38, no. 2 (2006), https://pubmed.ncbi.nlm.nih.gov/16429160/.

[299] Ryan D. McAllister et al., "Susceptibility to Anthrax Lethal Toxin Is Controlled by Three Linked Quantitative Trait Loci," *The American Journal of Pathology* 163, no. 5 (2003), https://doi.org/10.1016/S0002-9440(10)63532-8.

2. Coxiella burnetii

The bacteria *C. burnetii* is an intracellular pathogen, and the causative agent of Q fever. About 40 percent of people infected with *C. burnetii* become symptomatic and 1-3 percent of these develop chronic Q fever.[300]

Various host factors affect the progression of Q fever, from genetic factors to congenital disorders. The expression of the chemokine CXCL9 was found to be increased in chronic Q fever patients, indicating its potential for to be a biomarker for diagnosis of chronic Q fever.[301] A study by Jansen et al. used univariate logistic regression models to identify SNPs correlated with innate responses to *C. burnetii* such as cytokine production and basal reactive oxygen species production.[302] Two SNPs were associated with the development of Q fever, and four were identified as having potential protective effects. This information may be used to predict progression of disease. A major morbidity in chronic Q fever is endocarditis, which can be more frequently associated with congenital bicuspid aortic valves (the most frequent congenital heart disorder), which itself has a large heritable component.[303] Chronic adverse effects are usually seen in those with comorbidities who would not typically match an active-duty individual's profile, but similar studies in the future may help classify military populations based on susceptibility.

3. Ebola

Ebola Virus Disease is one of the more well-characterized infectious diseases when it comes to precision medicine. Various association studies have been performed to characterize the disease, identifying the underlying pathology and predicting outcomes. Host factors appear to play a large role in disease progression.

For instance, the genotypes and haplotypes of KIR (killer immunoglobulin-like receptor) have been associated with fatal outcomes. KIR genes exhibit a large amount of sequence diversity, with 70 and 33 alleles respectively having been described for KIR2DS1 and KIR2DS2 (members of the KIR family of genes).[304] Two haplotypes for KIR are common: haplotype A, which has seven KIR genes including a unique activating KIR gene KIR2DS4, and haplotype B which has

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[300] M. Maurin and D. Raoult, "Q Fever," *Clinical Microbiology Reviews* 12, no. 4 (1999), https://doi.org/10.1128/CMR.12.4.518.

[301] Anne F. M. Jansen et al., "CXCL9, a Promising Biomarker in the Diagnosis of Chronic Q Fever," *BMC Infectious Diseases* 17, no. 1 (2017), https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2656-6.

[302] A. F. M. Jansen et al., "Genetic Variations in Innate Immunity Genes Affect Response to Coxiella Burnetii and Are Associated with Susceptibility to Chronic Q Fever," *Clinical Microbiology and Infection* 25, no. 5 (2019), https://www.sciencedirect.com/science/article/pii/S1198743X18305858.

[303] Carole Eldin et al., "From Q Fever to Coxiella Burnetii Infection: A Paradigm Change," *Clinical Microbiology Reviews* 30, no. 1 (2017), https://pubmed.ncbi.nlm.nih.gov/27856520/.

[304] James Robinson et al., "IPD--the Immuno Polymorphism Database," *Nucleic Acids Research* 41, D1 (2013), https://academic.oup.com/nar/article/41/D1/D1234/1062158?login=true.

high variability and includes additional activating KIR genes.[305] The presence of activating KIR2DS1 and KIR2DS3 genes were linked to fatal outcomes in the Wauquier et al. study.[306]

The Niemann-Pick C1 (NPC1) receptor, which is involved in glycoprotein-mediated entry of filoviruses into cells, is also believed to be a determinant of susceptibility to filovirus infection. An analysis of 10 naturally occurring missense SNPs in humans found that several SNPs may result in reduced susceptibility to filoviruses.[307]

Multiple biomarkers have also been identified that may predict disease progression/severity. Studies performed using data collected during the 2001 outbreak of Ebola hemorrhagic fever caused by Sudan Virus (SUDV) have identified multiple biomarkers correlated to disease outcome, most notably CD40L levels, which are linked to nonfatal outcomes.[308]Another study identified a four-protein biomarker panel (Histone H1-5, moesin, kininogen 1, and ribosomal protein L35) which could predict disease outcomes more accurately than viral load.[309]

Transcriptomic analyses have also been used to diagnose Ebola without identifying viral load, with 15 miRNAs discovered to be common among EBOV-infected humans and non-human primates (NHPs). Of these 15, eight were used to create a classifier that could identify infection status, even in pre-symptomatic cases.[310]

4. Lassa Fever Virus

It has been hypothesized that Lassa virus (LASV) may have been a driver of natural selection of humans in West African populations, and studies have found evidence for positive selection in LARGE gene and interleukin 21 genes, which are implicated in LASV infectivity and immunity.[311] The identified variants of these gene may confer resistance to LASV and may therefore help predict disease outcome.

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[305] Nadia Wauquier et al., "Association of KIR2DS1 and KIR2DS3 with Fatal Outcome in Ebola Virus Infection," *Immunogenetics* 62, 11-12 (2010), https://link.springer.com/article/10.1007/s00251-010-0480-x.

[306] Ibid.

[307] Tatsunari Kondoh et al., "Single-Nucleotide Polymorphisms in Human NPC1 Influence Filovirus Entry into Cells," *The Journal of Infectious Diseases* 218, suppl_5 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6927862.

[308] Anita K. McElroy et al., "Ebola Hemorrhagic Fever: Novel Biomarker Correlates of Clinical Outcome," *The Journal of Infectious Diseases* 210, no. 4 (2014), https://academic.oup.com/jid/article/210/4/558/2908498.

[309] Arthur Viodé et al., "Plasma Proteomic Analysis Distinguishes Severity Outcomes of Human Ebola Virus Disease," *mBio* 13, no. 3 (2022), https://doi.org/10.1128/mbio.00567-22.

[310] Janice Duy et al., "Circulating MicroRNA Profiles of Ebola Virus Infection," *Scientific Reports* 6, no. 1 (2016), https://www.nature.com/articles/srep24496.

[311] Kristian G. Andersen et al., "Genome-Wide Scans Provide Evidence for Positive Selection of Genes Implicated in Lassa Fever," *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 367, no. 1590 (2012), https://doi.org/10.1098/rstb.2011.0299.

5. Marburg Virus

As described in 3.3.c, polymorphisms in the Niemann-Pick C1 gene are thought to influence filovirus entry into cells.[312] These SNPs may therefore also affect susceptibility to Marburg virus.

6. Ricin

Ricin is a naturally occurring toxin derived from the beans of the castor oil plant *Ricinus communis.*[313] The genes Fut9 and Slc35c1 have been identified as host factors required for ricin to exert its toxic effects in animal models.[314] Mutations in these genes therefore affect host susceptibility, even though this relationship has not yet been well characterized. The gene SLC35C1 is a protein coding gene which encodes a GDP-fucose transporter. In one study, human patient cells with SLC35C1 deficiency were found to be resistant to ricin, due to the masking of ricin-binding sites following increased sialylation of Lewis X structures (a carbohydrate present on cell surfaces which plays a role in cell recognition).[315] Human patients lacking SLC35C1 suffer from a diverse range of symptoms, including severe immunological deficiencies; however, this study offers insight into potential biomarkers for future studies to focus on.

7. Organophosphates

The paraoxonase genes PON1, PON2, PON3 have anti-oxidative properties, with PON1 involved in the metabolism of organophosphate (OP) compounds.[316] The 192R and 55L polymorphisms in the PON1 gene appear to be involved in susceptibility to OP poisoning; however, further research is required before it may be used as a biomarker.[317]

The 57 known CYP genes in the P450 gene family are also involved in OP metabolism, and hepatic P450-mediated metabolism represents the primary method of xenobiotic elimination from the body.[318] CYP2B6 is considered the primary enzyme for inactivation of many organophosphate pesticides, and studies have found multiple variants of the CYP2B6 gene, with individuals with

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[312] Kondoh et al., "Single-Nucleotide Polymorphisms in Human NPC1 Influence Filovirus Entry Into Cells."

[313] Sally M. Bradberry et al., "Ricin Poisoning," *Toxicological Reviews* 22, no. 1 (2003), https://link.springer.com/article/10.2165/00139709-200322010-00007.

[314] Ulrich Elling et al., "Forward and Reverse Genetics Through Derivation of Haploid Mouse Embryonic Stem Cells," *Cell Stem Cell* 9, no. 6 (2011), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008724.

[315] Jasmin Taubenschmid et al., "A Vital Sugar Code for Ricin Toxicity," *Cell Research* 27, no. 11 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674155/.

[316] Efthimios Dardiotis et al., "Paraoxonase-1 Genetic Polymorphisms in Organophosphate Metabolism," *Toxicology* 411 (2019), https://www.sciencedirect.com/science/article/pii/S0300483X18304803.

[317] Ibid.

[318] Gurpreet Kaur, A.K. Jain, and Sandeep Singh, "CYP/PON Genetic Variations as Determinant of Organophosphate Pesticides Toxicity," *Journal of Genetics* 96, no. 1 (2017), https://link.springer.com/article/10.1007/s12041-017-0741-7#Sec5.

the CYP2B6.6 potentially having a more robust ability to inactivate organophosphates.[319,320] This information could be used to predict an individual's clinical progression, if the genotype is known.

8. Influenza

HLA Class I alleles and haplotypes were demonstrated to be linked to susceptibility to the Influenza A (H1N1) 2009 virus.[321] SNPs in multiple genes such as FCGR2A, C1QBP, CD55, and RPAIN are thought to affect host immune response.[322] SNPs in other genes such as Il1B, TNF, LTA IL17A, IL8, and IL6 among others are associated with altered phenotypes in pro-inflammatory molecules, which participate in Influenza A infections.[323] With this information, a potential gene panel can be created which could predict an individual's response to infection, highlighting patients who are at higher risk.

9. Enterobacteriaceae

Carbapenem-resistance *Enterobacteriaceae* (CRE) have been designated by the U.S. CDC as a "nightmare bacteria" in light of their potential impact on human health.[324] CRE are usually resistant to all commercially available beta-lactams, as well as a number of other antibiotics, including fluoroquinolones. Reliable antibiotic activity against CRE is seen only with tigecycline, polymyxin B, and polymyxin E (colistin). Use of these drugs is often problematic. Colistin, for example, has a narrow therapeutic window (2µg/mL steady state is required, but renal toxicity occurs at 2.5µg/mL).[325] TDM might assist in guiding use of this toxic drug and is expanded on in 3.1.c.2).

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[319] Alice L. Crane et al., "Effect of CYP2B6*6 and CYP2C19*2 Genotype on Chlorpyrifos Metabolism," *Toxicology* 293, 1-3 (2012), https://doi.org/10.1016/j.tox.2012.01.006.

[320] Thomas Lang et al., "Extensive Genetic Polymorphism in the Human CYP2B6 Gene with Impact on Expression and Function in Human Liver," *Pharmacogenetics* 11, no. 5 (2001), https://doi.org/10.1097/00008571-200107000-00004.

[321] Ramcés Falfán-Valencia et al., "An Increased Frequency in HLA Class I Alleles and Haplotypes Suggests Genetic Susceptibility to Influenza a (H1N1) 2009 Pandemic: A Case-Control Study," *Journal of Immunology Research* 2018 (2018), https://www.hindawi.com/journals/jir/2018/3174868/.

[322] Gloria Pérez-Rubio et al., "Role of the Host Genetic Susceptibility to 2009 Pandemic Influenza a H1N1," *Viruses* 13, no. 2 (2021), https://www.mdpi.com/1999-4915/13/2/344.

[323] Ibid.

[324] Centers for Disease Control, "CDC: Action Needed Now to Halt Spread of Deadly Bacteria," March 5, 2013, https://www.cdc.gov/media/releases/2013/p0305_deadly_bacteria.html.

[325] Federico Perez et al., "Treatment Options for Infections Caused by Carbapenem-Resistant Enterobacteriaceae: Can We Apply "Precision Medicine" to Antimicrobial Chemotherapy?," *Expert Opinion on Pharmacotherapy* 17, no. 6 (2016), https://doi.org/10.1517/14656566.2016.1145658.

10. Tuberculosis

Gene sequencing panels have shown to produce faster results for drug susceptibility testing (DST) compared to traditional DSTs.[326] Mendelian susceptibility to mycobacterial disease (MSMD) is a rare condition characterized by predisposition to clinical disease by weakly virulent mycobacteria, but can also increase susceptibility to salmonellosis, candidiasis, and other bacteria, fungi, or viruses.[327] There have been nine MSMD-causing genes identified, all of which involve IFN-gamma-dependent immunity, impairing the production or response of IFN-gamma. Screening for these genes can identify individuals at higher risk for TB, along with salmonella and other infections. Genome-wise association studies have also identified loci for active tuberculosis susceptibility, which may be useful in gene panels.[328,329]

11. COVID-19

As noted in Table 9, by far the infectious disease with the highest number of genomics-related studies is COVID-19. COVID-19 is not thought of as a biological agent relevant for the battlefield, but this section is meant to represent how the large amount of data created due to COVID-19 has advanced precision medicine among various domains. This section reflects Chapter 3.1, providing an overview of studies analyzing various diagnostic targets in the context of COVID-19. Many of these concepts are applicable to other infectious diseases or even non-infectious diseases, such as in studies involving generalized inflammation, which may occur in various conditions.

a. Genome

Some of the first papers which described the effect of host genomics on susceptibility to COVID-19 or severity of COVID-19 symptoms largely used genome-wide association studies (GWAS) to determine potential loci of interest. Ellinghaus et al. published a GWAS in 2020 which found associations with COVID-19 severity at two loci: 3p21.31 and 9q34.2.[330] The signal at 3p21.31 coincided with the gene LZTFL1 and the signal at 9q34.2 coincided with the ABO blood type group. A later study found that LZTFL1 regulated a viral response pathway in pulmonary

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[326] Silke Feuerriegel et al., "Rapid Genomic First- and Second-Line Drug Resistance Prediction from Clinical Mycobacterium Tuberculosis Specimens Using Deeplex-MycTB," *European Respiratory Journal* 57, no. 1 (2021), https://doi.org/10.1183/13993003.01796-2020.

[327] Jacinta Bustamante et al., "Mendelian Susceptibility to Mycobacterial Disease: Genetic, Immunological, and Clinical Features of Inborn Errors of IFN-Γ Immunity," *Seminars in Immunology* 26, no. 6 (2014), https://www.sciencedirect.com/science/article/pii/S1044532314000906.

[328] Thorsten Thye et al., "Common Variants at 11p13 Are Associated with Susceptibility to Tuberculosis," *Nature Genetics* 44, no. 3 (2012), https://pubmed.ncbi.nlm.nih.gov/22306650/.

[329] Thorsten Thye et al., "Genome-Wide Association Analyses Identifies a Susceptibility Locus for Tuberculosis on Chromosome 18q11.2," *Nature Genetics* 42, no. 9 (2010), https://pubmed.ncbi.nlm.nih.gov/20694014/.

[330] David Ellinghaus et al., "Genomewide Association Study of Severe Covid-19 with Respiratory Failure," *The New England Journal of Medicine* 383, no. 16 (2020), https://doi.org/10.1056/NEJMoa2020283.

epithelial cells and a gain-of-function risk A allele for that gene was the probable cause of the association with this locus.[331] Other studies also found a link between blood type and COVID-19 diagnosis.[332] A later study by Butler-Laporte et al. found a deleterious variant in the SARS-COV2 sensor toll-like receptor TLR7, found on the X chromosome, which was associated with a five-fold increase in severe disease.[333]

As noted previously, it is important to use data from different populations for GWAS to avoid bias or finding associations indicative of only one group. For example, the OAS1/2/3 cluster is a risk locus for severe COVID-19.[334] This cluster originated within Neanderthals and therefore is prevalent mostly in those with European ancestry. Fine-mapping of those with African ancestry and European ancestry further showed that the differences in this locus and corresponding associations with COVID-19 severity can be correlated with ancestry.[335] Other gene associations, such as with TLR7 and MARK1, have also been driven largely by study participants with European ancestry.[336] A study by Chinese investigators also found that some of the associations previously observed in European populations were not the same as those observed in their Chinese participants.[337]

Other genomics studies have tested more specific hypotheses or focused on narrower symptoms of COVID-19 than just overall symptom severity or susceptibility GWAS studies. Shelton et al. used online surveys and multi-ancestry GWAS to identify the UGT2A1 and UGT2A2 genes as correlated with COVID-19-related loss of smell or taste.[338] Both of these genes are expressed in the olfactory epithelium and help metabolize odorants. Therefore, this could show a genetic link to the COVD-19-related loss of smell or taste. Butler-Laporte et al. used GWAS results to determine whether circulating Vitamin D levels influenced COVID-19 severity.[339] They

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[331] Damien J. Downes et al., "Identification of LZTFL1 as a Candidate Effector Gene at a COVID-19 Risk Locus," *Nature Genetics* 53, no. 11 (2021), https://doi.org/10.1038/s41588-021-00955-3.

[332] Janie F. Shelton et al., "The UGT2A1/UGT2A2 Locus Is Associated with COVID-19-Related Loss of Smell or Taste," *Nature Genetics* 54, no. 2 (2022), https://www.nature.com/articles/s41588-021-00986-w.

[333] Guillaume Butler-Laporte et al., "Exome-Wide Association Study to Identify Rare Variants Influencing COVID-19 Outcomes: Results from the Host Genetics Initiative," *PLOS Genetics* 18, no. 11 (2022), https://doi.org/10.1371/journal.pgen.1010367.

[334] Jennifer E. Huffman et al., "Multi-Ancestry Fine Mapping Implicates OAS1 Splicing in Risk of Severe COVID-19," *Nature Genetics* 54, no. 2 (2022), https://doi.org/10.1038/s41588-021-00996-8.

[335] Huffman et al., "Multi-Ancestry Fine Mapping Implicates OAS1 Splicing in Risk of Severe COVID-19."

[336] Butler-Laporte et al., "Exome-Wide Association Study to Identify Rare Variants Influencing COVID-19 Outcomes: Results from the Host Genetics Initiative."

[337] Yuanfeng Li et al., "Genome-Wide Association Study of COVID-19 Severity Among the Chinese Population," *Cell Discovery* 7, no. 1 (2021), https://doi.org/10.1038/s41421-021-00318-6.

[338] Shelton et al., "The UGT2A1/UGT2A2 Locus Is Associated with COVID-19-Related Loss of Smell or Taste."

[339] Guillaume Butler-Laporte et al., "Vitamin D and COVID-19 Susceptibility and Severity in the COVID-19 Host Genetics Initiative: A Mendelian Randomization Study," *PLOS Medicine* 18, no. 6 (2021), https://doi.org/10.1371/journal.pmed.1003605.

found that there was no correlation between genetically increased Vitamin D levels and COVID-19 susceptibility, hospitalization, or severe disease.

For more information or studies, the CDC produces a COVID Genomics and Precision Health database (COVID-19 GPH) which maintains thousands of publications related to pathogen and human genomics and other areas of interest for precision medicine related to COVID-19.[340] The database also produces a weekly update each Thursday on the new articles related to the topic.[341] In addition to this database, there have been some review articles and meta-analyses related to GWAS for COVID-19.

Cen et al. produced a good review of recent papers on precision medicine concepts related to COVID-19, including genomics, proteomics, and metabolomics.[342] The COVID-19 Host Genetics Initiative also published a meta-analysis of GWAS studies containing over 125,000 cases of COVID-19 and over 2.5 million controls across 60 studies.[343] The team found 11 more genome-wide significant loci than those previously identified, and found that all but one of the previously discovered loci increased their statistical significance as the additional data was included.

b. Epigenome

Several studies have been performed to determine the methylation signatures of COVID-19 infection. Most of these studies have been larger epigenome-wide association studies (EWAS) which looked at the methylation signatures of blood samples taken from those with or without COVID-19 or those with mild versus severe COVID-19.[344] Some of the studies found dozens of methylation sites related to COVID-19 disease or severity.[345,346] Therefore, we will not discuss each site in detail from those studies.

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[340] Wei Yu et al., "COVID-19 GPH: Tracking the Contribution of Genomics and Precision Health to the COVID-19 Pandemic Response," *BMC Infectious Diseases* 22, no. 1 (2022), https://doi.org/10.1186/s12879-022-07219-3.

[341] "COVID-19 Weekly Update: Up to Date Genomics and Precision Health Information on COVID-19," Centers for Disease Control and Prevention Website, accessed March 9, 2023, https://phgkb.cdc.gov/PHGKB/coVInfoClip.action?action=home#.

[342] Xiaoping Cen et al., "Towards Precision Medicine: Omics Approach for COVID-19," *Biosafety and Health*, 2023, https://doi.org/10.1016/j.bsheal.2023.01.002.

[343] "The COVID-19 Host Genetics Initiative, a Global Initiative to Elucidate the Role of Host Genetic Factors in Susceptibility and Severity of the SARS-CoV-2 Virus Pandemic," *European Journal of Human Genetics EJHG* 28, no. 6 (2020), https://doi.org/10.1038/s41431-020-0636-6.

[344] Swati Bhat, Praveen Rishi, and Vijayta D. Chadha, "Understanding the Epigenetic Mechanisms in SARS CoV-2 Infection and Potential Therapeutic Approaches," *Virus Research* 318 (2022), https://doi.org/10.1016/j.virusres.2022.198853.

[345] Manuel Castro de Moura et al., "Epigenome-Wide Association Study of COVID-19 Severity with Respiratory Failure," *eBioMedicine* 66 (2021), https://doi.org/10.1016/j.ebiom.2021.103339.

[346] Iain R. Konigsberg et al., "Host Methylation Predicts SARS-CoV-2 Infection and Clinical Outcome," *Communications Medicine* 1, no. 1 (2021), https://doi.org/10.1038/s43856-021-00042-y.

Many of the methylation sites were related to the immune system. Bowler et al. found those with COVID-19 had differences in four unique methylation sites – IFI27, EPSI1, IRF7, and cg07878065 – all of which (except cg07878065, which has an unknown function) are related to immune system function.[347] Guillermo et al. found that mild and severe cases could be distinguished via methylation of genes associated with IL-6.[348] Bradic et al. focused on those with COVID-19 who were on ventilators.[349] They found there were differences in methylation of immune system genes between those who died from COVID-19 and those who survived, but most of those differences were only observed toward the end of life. These studies indicate that there could be a number of epigenetic signatures which could be indicative of COVID-19 infection or severity. More studies would be needed, however, to determine how generalizable the results are or whether they could be used for precision medicine. Most of the studies used fewer than 500 patients (including both test subjects and controls).

c. Transcriptomics

Transcriptomic studies have been useful in analyzing the pathogenesis of SARS-CoV-2, as well as measuring disease progression and diagnosing individuals. The creation of large transcriptomic databases with appropriate metadata including clinical symptoms can allow for the creation of tools to implement precision medicine concepts against disease. Most of the studies identified that perform transcriptomic analyses for COVID-19 focus on tracking disease progression, estimating outcomes, and identifying relevant biomarkers.

A study that performed scRNA-seq to 284 samples from 196 COVID-19 patients and controls (a total of 1.46 million cells) created a database that could help identify immune subtype changes associated with clinical features, including severity and stage of disease.[350] The study could also identify how upregulation of the S100A8/A9 proteins by megakaryocytes and monocytes in peripheral blood could contribute to cytokine storms observed in severe disease, acting as a predictor for worse disease outcomes. Transcriptomic analyses can also identify the mechanisms behind disease progression, linking gene expression signatures with pathophysiological events. For instance, a study performed by Bagh identified specific COVID-19 mechanisms dysregulated

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[347] Scott Bowler et al., "A Machine Learning Approach Utilizing DNA Methylation as an Accurate Classifier of COVID-19 Disease Severity," *Scientific Reports* 12, no. 1 (2022), https://doi.org/10.1038/s41598-022-22201-4.

[348] Guillermo Barturen et al., "Whole-Blood DNA Methylation Analysis Reveals Respiratory Environmental Traits Involved in COVID-19 Severity Following SARS-CoV-2 Infection," *Nature Communications* 13 (2021), https://doi.org/10.1101/2021.11.03.21260184.

[349] Martina Bradic et al., "DNA Methylation Predicts the Outcome of COVID-19 Patients with Acute Respiratory Distress Syndrome," *Journal of Translational Medicine* 20, no. 1 (2022), https://doi.org/10.1186/s12967-022-03737-5.

[350] Xianwen Ren et al., "COVID-19 Immune Features Revealed by a Large-Scale Single-Cell Transcriptome Atlas," *Cell* 184, no. 7 (2021), https://doi.org/10.1016/j.cell.2021.01.053.

between different disease severity groups.[351] These mechanisms had transcriptomic signatures that overlapped with previously known organ dysfunction and sepsis signatures. Previously known signatures such as the so-called "cellular-reprogramming" signature were found to act as strong discriminators between different groups of disease severity. In severe cases, it was found that the 30-day mortality prediction was fairly accurate when using a known mortality transcriptomic signature of all-cause sepsis, potentially identifying how existing tools can be used for treatment/prognosis of patients.

As is common with many studies analyzing transcriptomic and other omics databases, machine learning methods have found success in identifying predictive biomarkers. Li et al. demonstrate the use of feature analysis methods (Boruta and the minimum redundancy maximum relevance methods) to identify markers to predict disease stages.[352] Similar techniques could also be applied for diagnosis of disease, and it was discovered that the immune system transcriptomic profile of SARS-CoV-2 had distinct signatures based on tissue type (i.e., a difference between nasopharyngeal swabs and whole blood samples).[353] The authors of this study proposed a biomarker panel that could distinguish SARS-CoV-2 infections based on transcriptomic profiles – with successful discrimination of COVID-19 patients from non-COVID patients – and the presence of predictive biomarkers for severe disease and increased inflammatory response.

d. Proteome

COVID infection can affect "inflammation, immune cell migration and degranulation, complement system, coagulation cascades, and energy metabolism," which can be characterized and analyzed with proteome biomarkers.[354] Proteomics is "in principle an ideal technology for systems-wide characterization of disease response," though it faces numerous challenges in real-world applications.[355] Samples used for proteomics can include serum, nasopharyngeal, and urine samples. The proteome can be analyzed using a variety of techniques and technologies, including MS methodologies (LC-MS, DIA-MS) and non-MS methodologies (proximity extension assay,

[351] Arjun Baghela et al., "Predicting Severity in COVID-19 Disease Using Sepsis Blood Gene Expression Signatures," *Scientific Reports* 13, no. 1 (2023), https://doi.org/10.1038/s41598-023-28259-y.

[352] Xiaohong Li et al., "Identification of Transcriptome Biomarkers for Severe COVID-19 with Machine Learning Methods," *Biomolecules* 12, no. 12 (2022), https://doi.org/10.3390/biom12121735.

[353] Samaneh Maleknia et al., "Identifying Novel Host-Based Diagnostic Biomarker Panels for COVID-19: A Whole-Blood/nasopharyngeal Transcriptome Meta-Analysis," *Molecular Medicine* 28, no. 1 (2022), https://doi.org/10.1186/s10020-022-00513-5.

[354] Michele Costanzo et al., "COVIDomics: The Proteomic and Metabolomic Signatures of COVID-19," *International Journal of Molecular Sciences* 23, no. 5 (2022), https://doi.org/10.3390/ijms23052414.

[355] Philipp E. Geyer et al., "High-Resolution Serum Proteome Trajectories in COVID-19 Reveal Patient-Specific Seroconversion," *EMBO Molecular Medicine* 13, no. 8 (2021), https://doi.org/10.15252/emmm.202114167.

protein immunoassay),[356] and LC-timsTOF (trapped ion mobility time-of-flight MS).[357] Furthermore, machine learning is often used to analyze proteomics data.[358,359,360] However, it must be noted that many COVID-specific proteomics studies are limited by small sample sizes.[361]

It has been observed that in COVID patients, "the levels of complement components and inflammation proteins tended to increase, whereas proteins of the coagulation cascade tended to decrease when compared to control groups."[362] One study identified 14 inflammatory proteins associated with COVID disease; among these, three proteins – IL-6, IL-10, and CXCL10 – were also observed to be a potential combination of biomarkers for predicting disease severity.[363] Costanzo et al. not only identified proteins that were associated with SARS-CoV-2 infection, but also proteins that may help distinguish disease outcomes. It was found that the proteins ORM1, ORM2, S100A9, CRP, AZGP1, CFI, SERPINA3/ACT, and LCP1/LPL were significantly up-regulated in severe COVID-19 cases, and the proteins FETUB, CETP, and PI16 were down-regulated in severe cases. In serum, common up-regulated proteins also include CXCL10, IL-6, and TNF.[364]

Geyer et al. compared COVID patients against PCR-negative patients with COVID-like symptoms over an average of 31 days to determine a proteome profile associated with COVID. They found that the most-decreased proteins were complement factors (e.g., C2, CFB), inflammatory proteins, and innate immunity mediators, while the most-increased were coagulation modulators (e.g., FN1, APOH), immunoglobulins, and some proteins involved in lipid homeostasis. The first significant changes to the proteome began to appear at days 6-10 after hospital admission.[365] Tushir et al. identified proteins unique to COVID disease in nasopharyngeal swabs that indicated increases in immune proteins – typically associated with neutrophil activation and degranulation proteins – as well as proteins related to oxidative stress and metabolic

[356] Costanzo et al., "COVIDomics: The Proteomic and Metabolomic Signatures of COVID-19."

[357] Geyer et al., "High-Resolution Serum Proteome Trajectories in COVID-19 Reveal Patient-Specific Seroconversion."

[358] Costanzo et al., "COVIDomics: The Proteomic and Metabolomic Signatures of COVID-19."

[359] Franziska Völlmy et al., "A Serum Proteome Signature to Predict Mortality in Severe COVID-19 Patients," *Life Science Alliance* 4, no. 9 (2021), https://doi.org/10.26508/lsa.202101099.

[360] Geyer et al., "High-Resolution Serum Proteome Trajectories in COVID-19 Reveal Patient-Specific Seroconversion."

[361] Yanchang Li et al., "Urine Proteome of COVID-19 Patients," *Urine* 2 (2020), https://doi.org/10.1016/j.urine.2021.02.001.

[362] Geyer et al., "High-Resolution Serum Proteome Trajectories in COVID-19 Reveal Patient-Specific Seroconversion."

[363] Costanzo et al., "COVIDomics: The Proteomic and Metabolomic Signatures of COVID-19."

[364] Ibid.

[365] Geyer et al., "High-Resolution Serum Proteome Trajectories in COVID-19 Reveal Patient-Specific Seroconversion."

pathways.[366] These protein profiles can provide a better understanding of the pathology of how COVID disease affects different body systems and processes.

Another study found that around 12-15 serum proteins could be used to distinguish between survivors and non-survivors at an early time point after hospital admission. Non-survivors tended to have higher levels of neutrophil pathway proteins, IgA, and SERPINA3, and significantly lower levels of type-3 cystatins HRG and FETUB compared to survivors. These proteins may be involved in innate immunity signaling and wound healing. Inter-α-trypsin inhibitors ITIH1 and ITIH2 were increased in survivors and tended to increase as the disease progressed; however, ITIH3 and ITIH4 were lower in survivors and tended to decrease over time.

However, other studies have found that SERPINA3, ITIH3, and ITIH4 increase in COVID patients and HRG and FN1 decrease in COVID patients compared to healthy controls, the latter of which slightly contrasts Völlmy et al.'s findings. This demonstrates that while protein panels may have decent predictability for outcomes, they are not universally true and tend to be better predictors earlier in the course of disease progression.[367]

Park et al. examined urine samples and found that IL-6 expression, which is related to inflammation, was within normal range for mild patients but was higher in severe patients and "drastically fluctuated during the infection."[368] They found that while protein profiles of COVID patients may change drastically over time, most protein levels return to normal by the time of recovery, as recovered patients' protein profiles matched well with those of healthy controls.

Park et al. also identified 44 proteins unique to mild COVID and 95 unique to severe COVID; compared to the mild cases, severe patients had increased levels of proteins that are highly associated with complement activation, immune regulation, and oxidative stress response, while the down-regulated proteins were associated with lipid metabolism and homeostasis, platelet degranulation, glucose and protein metabolism.[369] This suggests that severe cases have more systemic inflammation and cell responses, as well as hampered immune response and normal cell function. Additionally, other studies have found that the neutrophil, complement, and coagulant pathways could be significant differentials between mild and severe COVID cases.[370]

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[366] Sheetal Tushir et al., "Proteo-Genomic Analysis of SARS-CoV-2: A Clinical Landscape of Single-Nucleotide Polymorphisms, COVID-19 Proteome, and Host Responses," *Journal of Proteome Research* 20, no. 3 (2021), https://doi.org/10.1021/acs.jproteome.0c00808.

[367] Völlmy et al., "A Serum Proteome Signature to Predict Mortality in Severe COVID-19 Patients."

[368] Li et al., "Urine Proteome of COVID-19 Patients."

[369] Ibid.

[370] Joonho Park et al., "In-Depth Blood Proteome Profiling Analysis Revealed Distinct Functional Characteristics of Plasma Proteins Between Severe and Non-Severe COVID-19 Patients," *Scientific Reports* 10, no. 1 (2020), https://doi.org/10.1038/s41598-020-80120-8.

e. Microbiome

Growing evidence indicates that the gut microbiome contributes to the host immune response for infectious diseases, and multiple studies have looked into the role of the gut microbiome in COVID-19 infections. The gut microbiome is now thought to play an important role in many physiological functions including immune system modulation, and metagenomic studies on microbiomes in COVID-19 patients have added evidence to this theory.

A study that analyzed 11,584 metagenome-assembled genomes found that COVID-19 infection was associated with a reduction of strain richness of many species in the gut, and the gut microbiome profile could also be used to distinguish infections from healthy controls, as well as predict disease progression.[371] This study also identified a specific cohort of gut microbiome species which could diagnose COVID-19 across separate human population cohorts independent of host genetics and environmental factors, suggesting a role of some microbes in the pathogenesis of SARS-CoV-2.

Gut microbiome changes have also been linked to specific host responses, such as the microbe *C. comes* being correlated with $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts.[372] Sun et al. found that an abundance of *B. contaminans* was correlated with higher inflammation markers and a lower immune cell count, and identified multiple species associated with severe disease.[373] Moreover, microbiome changes were not limited to the gut microbiome; analyses of the oral microbiome have also shown how various microorganisms, such as abundance of members of the genera *Provotella* and *Veillonella,* are associated with prolonged COVID symptoms.[374]

Outside of acting as a diagnostic/prognostic tool, the microbiome can act as a target or guide for treatment to minimize the impact of disease. It has been suggested that intestinal microbiome dysbiosis, which can result due to SARS-CoV-2, may play a large factor in severe disease and mortality in at-risk groups such as elderly patients, and efforts to control microbiome dysbiosis may help better clinical outcomes.[375] A randomized trial performed in 293 individuals showed a

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[371] Shanlin Ke, Scott T. Weiss, and Yang-Yu Liu, "Dissecting the Role of the Human Microbiome in COVID-19 via Metagenome-Assembled Genomes," *Nature Communications* 13, no. 1 (2022), https://doi.org/10.1038/s41467-022-32991-w.

[372] Xiaoguang Xu et al., "Integrated Analysis of Gut Microbiome and Host Immune Responses in COVID-19," *Frontiers of Medicine* 16, no. 2 (2022), https://doi.org/10.1007/s11684-022-0921-6.

[373] Zhonghan Sun et al., "Gut Microbiome Alterations and Gut Barrier Dysfunction Are Associated with Host Immune Homeostasis in COVID-19 Patients," *BMC Medicine* 20, no. 1 (2022), https://doi.org/10.1186/s12916-021-02212-0.

[374] John P. Haran et al., "Inflammation-Type Dysbiosis of the Oral Microbiome Associates with the Duration of COVID-19 Symptoms and Long COVID," *JCI Insight* 6, no. 20 (2021), https://doi.org/10.1172/jci.insight.152346.

[375] Lubomír Janda, Matúš Mihalčin, and Michaela Šťastná, "Is a Healthy Microbiome Responsible for Lower Mortality in COVID-19?," *Biologia* 76, no. 2 (2021), https://doi.org/10.2478/s11756-020-00614-8.

significant difference in viral load, lung infiltrates, and duration of COVID-19 symptoms in individuals who were supplemented with a probiotic formula compared to the control.[376]

Traditional workflows for analyzing the microbiome may focus on bacterial DNA to identify micro-organisms, but organisms including fungi and viruses may also act as sources of information for omics studies. Being subsets of the microbiome, the mycobiome and virome are terms which refer to the sum of all fungi and viruses existing in an environment, respectively. These non-bacterial organisms can also interact with human physiology, and may play a role in the progression of disease.

COVID-19 also alters the intestinal fungal microbiome along with the bacterial microbiome, and various species have been identified that may act as markers of disease progression. For instance, *Candida spp.* were shown to increase in abundance in patients with acute respiratory distress syndrome, with an overall decrease in fungal diversity.[377] The gut virome is also affected by infections. The presence of SARS-CoV-2 RNA can be identified in fecal shotgun sequencing, but the relative abundances of other viral species may also change. One example is the pepper chlorotic spot virus, an RNA virus that was inversely correlated with COVID-19 severity, pro-inflammatory proteins, white cell counts, and neutrophil counts.[378]

f. Metabolome

The metabolic pathways include numerous signaling molecules, many of which can impact and regulate parts of the immune response. Various studies have shown that changes to the metabolome may be useful as biomarkers and predictors of COVID-19 disease severity.[379] Compared to the genome or even the proteome, the metabolome is "a more sensitive indicator" of the current status of cells or organs, as metabolites serve a very specific purpose and are short-lived molecules. This can aid in understanding or characterizing otherwise poorly understood processes.[380] Techniques used to analyze the metabolome and identify potential biomarkers can

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[376] Pedro Gutiérrez-Castrellón et al., "Probiotic Improves Symptomatic and Viral Clearance in Covid19 Outpatients: A Randomized, Quadruple-Blinded, Placebo-Controlled Trial," *Gut Microbes* 14, no. 1 (2022), https://doi.org/10.1080/19490976.2021.2018899.

[377] Elisa Viciani et al., "Critically Ill Patients with COVID-19 Show Lung Fungal Dysbiosis with Reduced Microbial Diversity in Patients Colonized with Candida Spp," *International Journal of Infectious Diseases* 117 (2022), https://doi.org/10.1016/j.ijid.2022.02.011.

[378] Tao Zuo et al., "Temporal Landscape of Human Gut RNA and DNA Virome in SARS-CoV-2 Infection and Severity," *Microbiome* 9, no. 1 (2021), https://doi.org/10.1186/s40168-021-01008-x.

[379] Ding Shi et al., "The Serum Metabolome of COVID-19 Patients Is Distinctive and Predictive," *Metabolism* 118 (2021), https://doi.org/10.1016/j.metabol.2021.154739.

[380] Ivayla Roberts et al., "Untargeted Metabolomics of COVID-19 Patient Serum Reveals Potential Prognostic Markers of Both Severity and Outcome," *Metabolomics* 18, no. 1 (2021), https://doi.org/10.1007/s11306-021-01859-3.

include GC-MS,[381,382] NMR, and MALDI-TOF.[383] Some emerging technologies, such as ambient ionization MS, may allow for clinical specimens to be analyzed as far-forward as the point of care with little to no sample preparation.[384]

One study identified 75 metabolites associated with SARS-CoV-2 infection; some metabolites were associated with respiratory infections (e.g., elevated levels of butyric acid, 2-hydroxybutyric acid, L-glutamic acid, L-phenylalanine, L-serine, L-lactic acid, and cholesterol), while some were *only* found in COVID patients (e.g., elevated levels of D-fructose and succinic acid, along with reduced levels of citric acid and 2-palmitoyl-glycerol). These unique distinguishing metabolites may aid in COVID diagnosis and understanding its pathogenesis.

It was also determined that comorbidities did not significantly impact the metabolome profile as compared to COVID infection. For example, D-fructose enhances dendritic cell inflammation, which is often observed in COVID patients. Shi et al. also identified a few metabolites that could distinguish between mild and severe COVID, though 2-hydroxybutyric acid was the only "good" predictor. Most metabolites returned to normal by the time of hospital discharge.[385]

Lv et al. identified nine distinguishing metabolites in COVID patients: sucrose, ribonic acid, and 2-palmitoyl-glycerol were significantly increased, while 2,4-di-tert-butylphenol, arachidic acid, behenic acid, pseudouridine, 7H-purine and D-allose were significantly decreased in COVID patients. The authors found that sucrose, lactic acid, ribonic acid, and 2-palmitoyl-glycerol[386] were good predictors of disease, with an area-under-the-curve of 0.7–0.85.

Interestingly, some of these metabolites are associated with GI bacteria and fungi, while some metabolites that were enriched are mostly or entirely derived from food; this provides insight into how COVID disrupts the body's metabolism and can impact nutrient absorption. Furthermore, other metabolites become enriched when there is a reduction in certain gut microbes, indicating a disease-induced disruption of the microbiome.[387]

Hasan et al. examined volatile organic compounds (VOC) in exhaled air. This method is non-invasive, allows for easy sample collection, and is especially useful for respiratory diseases. They

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[381] Shi et al., "The Serum Metabolome of COVID-19 Patients Is Distinctive and Predictive."

[382] Longxian Lv et al., "The Faecal Metabolome in COVID-19 Patients Is Altered and Associated with Clinical Features and Gut Microbes," *Analytica Chimica Acta* 1152 (2021), https://doi.org/10.1016/j.aca.2021.338267.

[383] Mohammad R. Hasan, Mohammed Suleiman, and Andrés Pérez-López, "Metabolomics in the Diagnosis and Prognosis of COVID-19," *Frontiers in Genetics* 12 (2021), https://doi.org/10.3389/fgene.2021.721556.

[384] Hasan, Suleiman and Pérez-López, "Metabolomics in the Diagnosis and Prognosis of COVID-19."

[385] Shi et al., "The Serum Metabolome of COVID-19 Patients Is Distinctive and Predictive."

[386] Note that Shi et al. also found 2-palmitoyl-glycerol to be a unique metabolite in COVID patients, although with the opposite level of expression.

[387] Lv et al., "The Faecal Metabolome in COVID-19 Patients Is Altered and Associated with Clinical Features and Gut Microbes."

found that detection of SARS-CoV-2 using this method ranged from 75 to 100 percent sensitivity and 66 to 96 percent specificity. Four VOCs were identified as unique to severe COVID: methylpent-2-enal, 2,4-octadiene, 1-chloroheptane, and nonanal, all significantly elevated. These metabolites may be distinguishing factors between milder cases. It has been noted that the arginine/kynurenine ratio is very good at predicting COVID, as the kynurenine pathway can impact IL-6 levels associated with COVID.[388] Costanzo et al. noted that tryptophan metabolism is impacted and associated with severe disease when tryptophan is converted to NAD (nicotinamide adenine dinucleotide) via the kynurenine pathway.[389]

Caterino et al. examined amino acid metabolism and increased levels of lactic acid in COVID patients. They identified increased levels of lactic acid, glutamate, aspartate, phenylalanine, β-alanine, ornithine, arachidonic acid, choline, and xanthine in both moderate and severe cases compared to healthy controls. SARS-CoV-2 infection seems to suppress adenosine triphosphate production and cause a shift from aerobic respiration to lactic fermentation; high levels of lactic acid have been associated with cases of sepsis and circulatory shock, both of which can occur in severe COVID disease. Furthermore, they found that TNF-α, IL-17 A, and IL-26 were the primary metabolites most associated with this shift.[390]

These studies and others indicate a growing interest in the metabolite profiles of COVID, but there is still limited research that provides clear and well-substantiated COVID metabolic profiles.[391] As Costanzo et al. state, "[a]lthough a great deal of effort was put into COVID-19 biomarker research and a number of potential biomarkers were identified, no large-scale trials were performed to reliably determine their usefulness in clinical setting."[392] If metabolite profiling is a desired clinical tool for diagnosing and characterizing COVID, more research and technology development must be performed.

g. Clinical History/Electronic Health Records

Traditionally, linking a patient's electronic health records across years and multiple institutions has been challenging for many health systems. Nationalized healthcare systems like the one in the United Kingdom have allowed researchers to conduct analyses across many different levels of care (e.g., primary care, hospitals, testing centers, national death records), linking data from diverse sources to track individuals through care systems. In response to the COVID-19

[388] Hasan, Suleiman and Pérez-López, "Metabolomics in the Diagnosis and Prognosis of COVID-19."

[389] Costanzo et al., "COVIDomics: The Proteomic and Metabolomic Signatures of COVID-19."

[390] Marianna Caterino et al., "The Serum Metabolome of Moderate and Severe COVID-19 Patients Reflects Possible Liver Alterations Involving Carbon and Nitrogen Metabolism," *International Journal of Molecular Sciences* 22, no. 17 (2021), https://doi.org/10.3390/ijms22179548.

[391] Hasan, Suleiman and Pérez-López, "Metabolomics in the Diagnosis and Prognosis of COVID-19."

[392] Hasan, Suleiman and Pérez-López, "Metabolomics in the Diagnosis and Prognosis of COVID-19."

pandemic, researchers have investigated disease trajectories (e.g., how patients interact with and move through the healthcare system) for patients in England.[393]

Based on this linked data, they categorized patients into COVID-19 phenotypes, including positive COVID-19 tests, COVID-19 diagnoses from primary care physicians, hospital admissions with COVID-19 diagnoses, respiratory support, and death. Any given patient could be categorized into multiple phenotypes. One finding showed mortality was highest among patients who required ventilation outside of intensive care units during the first wave of COVID (February 20-May 29, 2020).[394] They also associated mortality rates with vaccination status. This type of knowledge could enable earlier intervention for patients with risk factors or trigger examination of healthcare systems to improve outcomes.

Another benefit of examining longitudinal electronic health records is the ability to identify longer-term consequences of COVID-19 infection. Researchers used electronic health records from the U.S. Department of Veterans Affairs to identify and describe risk factors for developing post-acute sequelae of COVID-19 (i.e., long COVID).[395] One of their major findings was that risk for development of post-acute sequelae increased with the severity of acute COVID-19 infection (i.e., whether patients were not hospitalized, hospitalized, or admitted to intensive care units). They also characterized use of healthcare resources and medications by COVID-19 patients 30 days after their illness, finding that patients who recovered from acute COVID-19 were more likely to use these resources than non-COVID patients. These types of retrospective analyses could inform health planning and resource management.

The military population may be ideally suited to research on clinical history using electronic health records, as data collected by the military health system can be coordinated. For effective tracking of electronic health records among service members, interoperability between military and civilian health records will need to be considered.

h. Biobanking

Samples from patients who succumbed to or recovered from COVID-19 have been collected and stored in a variety of biobanks for future analysis. Biobanking efforts typically lead to advances in -omics associations, as they provide well-characterized samples from which

[393] Johan H. Thygesen et al., "COVID-19 Trajectories Among 57 Million Adults in England: A Cohort Study Using Electronic Health Records," *The Lancet Digital Health* 4, no. 7 (2022), https://doi.org/10.1016/S2589-7500(22)00091-7.

[394] Johan H. Thygesen et al., "COVID-19 Trajectories Among 57 Million Adults in England: A Cohort Study Using Electronic Health Records."

[395] Ziyad Al-Aly, Yan Xie, and Benjamin Bowe, "High-Dimensional Characterization of Post-Acute Sequelae of COVID-19," *Nature* 594, no. 7862 (2021), https://doi.org/10.1038/s41586-021-03553-9.

researchers can conduct their analyses.[396] These COVID-19 biobanks have been used to study a variety of topics, including genome-wide association studies to find risk variants associated with lethal SARS-CoV-2 infection[397] and long COVID.[398]

i. Radiomics

Considerable effort was dedicated to the development of imaging-based diagnostics for COVID-19, particularly when the availability of PCR and antigen tests was relatively limited (see Table 10). Computed tomography (CT) and X-ray equipment is available in most medical care facilities and may be beneficial for rapidly establishing diagnostic methods immediately following an outbreak for which biochemical testing methods are not available. Of these imaging methods, CT imaging is higher resolution, though X-ray imaging tends to be more widely available, affordable, and faster, and exposes patients to less radiation.[399] The majority of studies seemed to focus on the diagnosis of COVID-19 compared to other respiratory illness (e.g., influenza, pneumonia), with fewer studies investigating outcomes.

One notable exception was Wu et al., who developed an algorithm to use radiomic markers to predict whether a patient would be more likely to experience poor prognostic outcomes, including death, need for mechanical ventilation, or admission to an intensive care unit.[400] This type of analysis could lead to earlier intervention and improve patient outcomes and provides additional information that would not be available if only molecular-based diagnostic tools were used. Overall, radiomics seem unlikely to replace molecular assays as a diagnostic screening tool, but may be an important decision support tool for individuals who have already been hospitalized.

Table 10. Imaging-Based Diagnostics for COVID-19

Study	Imaging type	Groups	Prediction	Accuracy[a]
(Wu et al. 2020)	CT	Early stage (< 6 days after symptoms, n = 212) or later stage (>6	Poor prognostic outcomes (death, mechanical	86-98%

[396] Stephanie M. LaVergne et al., "A Longitudinal SARS-CoV-2 Biorepository for COVID-19 Survivors with and without Post-Acute Sequelae," *BMC Infectious Diseases* 21, no. 1 (2021), https://doi.org/10.1186/s12879-021-06359-2.

[397] Toni M. Delorey et al., "COVID-19 Tissue Atlases Reveal SARS-CoV-2 Pathology and Cellular Targets," *Nature* 595, no. 7865 (2021), https://doi.org/10.1038/s41586-021-03570-8.

[398] Stephanie M. LaVergne et al., "A Longitudinal SARS-CoV-2 Biorepository for COVID-19 Survivors with and without Post-Acute Sequelae."

[399] Jakub Kufel et al., "Application of Artificial Intelligence in Diagnosing COVID-19 Disease Symptoms on Chest X-Rays: A Systematic Review," *International Journal of Medical Sciences* 19, no. 12 (2022), https://doi.org/10.7150/ijms.76515.

[400] Qingxia Wu et al., "Radiomics Analysis of Computed Tomography Helps Predict Poor Prognostic Outcome in COVID-19," *Theranostics* 10, no. 16 (2020), https://doi.org/10.7150/thno.46428.

		days after symptoms, n = 105)	ventilation, ICU admission)	
(Chen et al. 2021)	CT	COVID patients (n = 108); other viral pneumonias (n = 77)	Diagnosing patients with COVID-19	0.915 (AUC)
(Zhang et al. 2021)	CT	COVID patients (n = 98); non-COVID pneumonia (n = 157); influenza/mycoplasma pneumonia patients (n = 38)	Diagnosing patients with COVID-19	92-96%
(Santone et al. 2021)	CT	Healthy patients; COVID patients; non-COVID pneumonia	Diagnosing patients with COVID-19	81%
(Wang et al. 2023)	X-ray	COVID patients (n = 1,245); healthy patients (n = 1,245); viral pneumonia (n = 1,225); bacterial pneumonia (n = 1,245)	Diagnosing patients with COVID-19	95%
(Chen and Rezaei 2021)	X-ray	COVID patients; healthy patients[b]	Diagnosing patients with COVID-19	86%
(Xia et al. 2021)	X-ray	COVID patients (n = 512); influenza patients (n = 106);	Diagnosing patients with COVID-19	0.971 (AUC)
(Sharifrazi et al. 2021)	X-ray	COVID patients (n = 77); healthy patients (n = 256)	Diagnosing patients with COVID-19	99%
(Tabik et al. 2020)	X-ray	COVID patients with mild (n = 100), moderate (n = 171) or severe (n = 79) symptoms; healthy patients (n = 426)	Diagnosing patients with severe, moderate, or mild COVID-19	98% (severe); 87% (moderate); 62% (mild)
(Joshi et al. 2021)	X-ray	COVID (n = 465); healthy (n = 1,077); bacterial pneumonia (n = 1,000); viral pneumonia (n = 1,000); other anomalies (n = 230)	Diagnosing patients with COVID-19	97%
(Mahmud, Rahman and Fattah 2020)	X-ray	COVID (n = 305); healthy (n = 305); bacterial pneumonia (n = 305); viral pneumonia (n = 305)	Diagnosing patients with COVID-19	90%

AUC = Area under the curve

[a] The accuracy reported in this table represents the value the paper reported for multimodal accuracy if the group was attempting to distinguish between multiple diseases (e.g., healthy, COVID-19, bacterial pneumonia, as opposed to bimodal (e.g., healthy vs COVID-19). Bimodal accuracies between COVID-19 and healthy patients always tended to be higher than multimodal accuracies.

[b] Source did not report the number of patients in each group.

Overall, radiomics may be a useful tool to supplement molecular diagnostics, particularly when molecular diagnostics may not be available. One potential hurdle with use of radiomics for biological agents, as opposed to diseases like COVID-19, is that a significant amount of imaging data is required to train models, which may not be practical with agents which are not commonly encountered.

4. Market Analysis

Investment in precision medicine and precision diagnostics has increased dramatically in recent years. One report valued the precision diagnostics market at roughly $78 billion in 2022; other estimates predict that will increase to $138-168 billion by 2028.[401,402] Due to the broad scope of precision medicine, companies involved with precision medicine typically span multiple domains. A large portion of precision medicine technologies are based on genomic technologies; therefore, many companies dealing with genomics technologies are likely positioned to be leaders of the field of precision medicine.

Table provides an overview of the top genome sequencing companies. Similarly, Table lists microbiome diagnostic companies with an analysis of their products, whether on the market or under development. A commercial technology of note is Oxford Nanopore's MinION sequencer, which is capable of portable genome sequencing, and has been tested in NATO field exercises for biological detection.[403,404]

An important point to consider when looking at the precision medicine market is that most companies do not specifically focus on infectious disease precision medicine. Most applications of precision medicine are either in other domains such as oncology, or are general-use such as sequencing technologies. To target infectious diseases / chemical and biological agents, currently existing technologies must be adapted for these diseases.

Equally relevant in the field of precision medicine are organizations which store, distribute, and analyze data. An example is the company Tempus, which has established partnerships with cancer centers across the United States to provide a proprietary platform which uses both unstructured data (such as clinical notes and pathology images) and structured data (sequencing

[401] "Precision Diagnostics Market Size, Share, and COVID-19 Impact Analysis," Fortune Business Insights Website, accessed November 10, 2022, https://www.fortunebusinessinsights.com/industry-reports/precision-diagnostics-market-100357.

[402] "Precision Diagnostics Market Growth Analysis: Report 2022-2028," The Insight Partners Website, accessed November 10, 2022, https://www.theinsightpartners.com/reports/precision-diagnostics-market.

[403] Fuentes-Chust et al., "The Microbiome Meets Nanotechnology: Opportunities and Challenges in Developing New Diagnostic Devices."

[404] Mathias C. Walter et al., "MinION as Part of a Biomedical Rapidly Deployable Laboratory," *Journal of Biotechnology* 250 (2017), https://pubmed.ncbi.nlm.nih.gov/27939320/.

data) to produce actionable personalized clinical insights.[405] Tempus was recently valued at $2 billion.[406] Geisinger Health System has partnered with Regeneron and, with an initial $100 million investment, aims to sequence and analyze 250,000 patient samples in order to act as a biobank to advance precision medicine.[407]

Table 11. Top Genome Sequencing Companies

Company Name	Revenue in 2017 (Billion USD)	Location
Illumina	2.8	California, U.S.
Thermo Fisher Scientific	0.42	Massachusetts, U.S.
BGI	0.33	Shenzhen, China
Agilent Technologies	0.23	California, U.S.
Qiagen	0.12	Hilden, Germany
Macrogen	0.095	Seoul, South Korea
Pacific Biosciences	0.094	California, U.S.
10x Genomics	0.71	California, U.S.
Oxford Nanopore Technologies	0.006	Oxford, U.K.

Source: Derived from Alex Philippidis, "Top 10 Sequencing Companies," *Genetic Engineering and Biotechnology News*, April 9, 2018, https://www.genengnews.com/topics/omics/top-10-sequencing-companies-2/.

Table 10. Biotechnology Companies with Microbiome Diagnostics Products Available or in Development

Company	Direct to consumer	Research	Therapeutics	IVD	Sample	Targets	Regulator	Status
Mbiome	X	XXX	X	X	Stool, mouth, nose, genitals and skin swabs	IBS, IBD, UC, Crohn's disease, HPV, STIs	FDA	Commercially available
CosmosID		XXX		X	Various	IVD, HAIs, pharmaceutical discovery, public health, food production,	Not yet regulated	NGS and bioinformatics services available

[405] "Tempus | Data-Driven Precision Medicine," Tempus Website, accessed November 18, 2022, https://www.tempus.com/.

[406] Jacob Aptekar et al., "Precision Medicine: Opening the Aperture," *McKinsey & Company*, February 6, 2019, https://www.mckinsey.com/industries/life-sciences/our-insights/precision-medicine-opening-the-aperture.

[407] "Geisingers MyCode Genomic Study Hits 100K Recruits Goal Now Set at 250K," Geisinger Website, accessed November 18, 2022, https://www.geisinger.org/about-geisinger/news-and-media/news-releases/2016/09/01/14/13/geisingers-mycode-genomic-study-hits-100k-recruits-goal-now-set-at-250k.

						environmental microbial detection		
Diversigen		XXX			Various	Crohn's disease, IBS, *C. difficile* infection	Not yet regulated	Research Use Only (RUO)
Enterome		XXX	X	X	Stool	IBD, Crohn's disease	FDA	Companion diagnostics in development
Epibiome		XXX	X		Various	Bacterial profiling	FDA	RUO
Genetic Analysis AS	X	XXX		X	Stool	IBS	CE	Approved
HolistX	X				Stool	Metabolism, diabetes, wound care	Not yet regulated	Commercially available
Metabiomics		XXX		X	Stool	Colon polyps, colorectal cancer	FDA	Preliminary clinical trial finalized
MetaboGen		XXX	x		Stool, blood	Obesity, diabetes, and atherosclerosis	Not yet regulated	Patent granted for diabetes prediction test
Nanopore		XXX			DNA/RNA	Non-specific	Not yet regulated	RUO
Thryve	X				Stool	Metabolism	Not yet regulated	Commercially available
Viome	X				Stool	Metabolism	Not yet regulated	Commercially available

Source: Derived from Diana R. Hernandez, "Gut Check: In Vitro Diagnostics for Gut Microbiome Analysis," *Clinical Microbiology Newsletter* 41, no. 7 (2019), https://www.sciencedirect.com/science/article/pii/S0196439919300261.

The precision medicine domain also includes pharmaceutical companies, who arguably have the largest stake in this space, and have been leading precision medicine treatments. In 2017 and 2018, the approval of Yescarta (Gilead Sciencs, Inc.) and Kymriah (Novartis) constituted landmark advances in the application of precision medicine.[408,409] As "personalized" treatments for leukemia and lymphoma, respectively, the therapies involve chimeric antigen receptor T-cells (CAR-T), a

[408] "YESCARTA (Axicabtagene Ciloleucel)," U.S. Food and Drug Administration Website, accessed November 18, 2022, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

[409] "KYMRIAH (Tisagenlecleucel)," U.S. Food and Drug Administration Website, accessed November 18, 2022, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel.

type of immunotherapy in which the patient's T-cells are genetically modified in order to target cancer cells.

A number of companies have also established niches in various omics domains. Metabolon, for instance, has developed a method that tests for inherited metabolic diseases using a small plasma sample and an untargeted metabolomics platform.[410,411] Biocrates' platform includes the p180 kit, a high-throughput metabolomic analysis component capable of detecting various analytes in multiple types of samples.[412] Biocrates' MxP Quant 500 kit targets detection of 630 metabolites using LC-MS/MS (for small molecules) and FIA-MS/MS (for lipids).[413] Similarly, in the proteomics domain, Somalogic has developed the SomaScan Assay, which implements plasma proteomics technology in order to stratify cardiovascular disease patients for risk of secondary events such as myocardial infarction or congestive heart failure.[414]

Companion diagnostics are diagnostic devices (typically based on biomarkers) that can be used to match a patient to an appropriate therapy.[415] There are currently over 150 companion diagnostic devices approved by the FDA. The vast majority of these devices focus on cancer, with only three devices (as of this writing) focused on other applications (thalassemia, aggressive systemic mastocytosis, and obesity).[416]

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[410] Ning Liu et al., "Comparison of Untargeted Metabolomic Profiling Vs Traditional Metabolic Screening to Identify Inborn Errors of Metabolism," *JAMA Network Open* 4, no. 7 (2021), https://doi.org/10.1001/jamanetworkopen.2021.14155.

[411] "A Metabolomic Approach to Better Clinical Diagnostics," Metabolon Website, accessed November 18, 2022, https://www.metabolon.com/blog/a-metabolomic-approach-to-better-clinical-diagnostics/.

[412] "AbsoluteIDQ P180 Kit - the Standard in Targeted Metabolomics," Biocrates Website, accessed November 18, 2022, https://biocrates.com/absoluteidq-p180-kit/.

[413] Xie et al., "A Metabolite Array Technology for Precision Medicine."

[414] "Proteomics and Heart Failure: Improving Risk Stratification and Treatment," SomaLogic Website, accessed November 18, 2022, https://somalogic.com/blog/proteomics-and-heart-failure-improving-risk-stratification-and-treatment.

[415] Peter Keeling, Jordan Clark, and Stephanie Finucane, "Challenges in the Clinical Implementation of Precision Medicine Companion Diagnostics," *Expert Review of Molecular Diagnostics* 20, no. 6 (2020), https://doi.org/10.1080/14737159.2020.1757436.

[416] "List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)," U.S. Food and Drug Administration Website, accessed November 10, 2022, https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

5. Future Paths

Precision medicine is a rapidly advancing field, but much work is still needed before precision medicine-based concepts can be widely applied to clinical diagnosis and treatment. This might be particularly true as it applies to chemical and biological agents, where advances lag far behind those in the field of oncology, for example. The advances are required in two major domains: first, there is a need for the generation of a large amount of data in order to identify actionable associations and stratify patients, and second, there is a need to enhance and modify diagnostic technologies in order to detect targets of precision medicine relevance.

A. Diverse populations

In order to establish associations that can be generalized and not necessarily focused in isolated populations, association studies must be performed in large, diverse populations. Until now, the majority of genomic association studies have been focused on people of European ancestry, which may cause unfavorable outcomes when using the information obtained on larger populations.[417] For example, a G6PD gene variant that is common (11 percent) in African populations but absent in the European populations is associated with decreased HbA1c levels, irrespective of blood glucose levels.[418] This could lead to underdiagnosis of type 2 diabetes in African ancestry populations if diagnosis is based on HbA1c levels alone. In order to adjust for variations, a large amount of data will be required, spanning multiple populations and diseases. This data includes omics and clinical data and can be generated through the various technologies described in this study.

B. Deep phenotypic characterization

Retrospectively and prospectively linking electronic health records (EHRs) with genetic and other omics data can lead to enhanced clinical characterization of conditions and enable discovery of new genetic associations. This can only be possible with the establishment of large-scale biobanks, such as the All of Us initiative, The Million Veterans Program and the UK Biobank, all of which contain information of several hundred thousand individuals, and have attempted linkage

[417] Alice B. Popejoy and Stephanie M. Fullerton, "Genomics Is Failing on Diversity," *Nature* 538, no. 7624 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089703.

[418] Eleanor Wheeler et al., "Impact of Common Genetic Determinants of Hemoglobin A1c on Type 2 Diabetes Risk and Diagnosis in Ancestrally Diverse Populations: A Transethnic Genome-Wide Meta-Analysis," *PLOS Medicine* 14, no. 9 (2017), https://doi.org/10.1371/journal.pmed.1002383.

to EHRs.[419] Theoretically, such databases would increase the ease of translation of precision medicine to the clinical world.

An example of the success of this concept is seen in the ANGPTL3 gene. Loss-of-function variants identified in the gene were associated with lower levels of serum triglycerides, HDL cholesterol, and LDL cholesterol, and subsequent studies in animal models found that targeted genetic and therapeutic antagonism of the gene could decrease odds of atherosclerotic disease.[420] The convergence of high-throughput technologies and electronic health records, along with proper policies to ensure responsible data handling, can enable unprecedented opportunities to derive new phenotypes form real-world clinical data. These phenotypes can both improve the diagnoses of disease variants and validate new treatments.[421]

C. Infectious diseases

As described previously, applying precision medicine concepts to infectious diseases is still a lagging field when compared to other disease domains such as cancers. However, potential exists for precision medicine to make a large impact on the outcomes of infectious diseases, by allowing for targeted treatment and targeted surveillance of patients, identifying those at higher risk, and more accurately predicting clinical outcomes.

The ultimate goal of precision medicine is to predict and prevent unfavorable clinical outcomes, which can be achieved by multiple methods. These same principles also translate to the application of precision medicine to chemical agents. The application of precision medicine in this domain will require well-phenotype human cohorts, with reductions in cost of processing each sample and an increased availability of associated technologies.

The immune system is one of the most complex biological systems in animals, and high-throughput profiling technologies, such as omics platforms, have enabled comprehensive characterization of components of this system at various scales.[422] COVID-19 is one of the best current examples for the application of precision medicine for infectious diseases. Included among the large amount of data collected during the pandemic are multiple genetic determinants of susceptibility to infection, including severe infection.[423]

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[419] Benjamin S. Glicksberg, Kipp W. Johnson, and Joel T. Dudley, "The Next Generation of Precision Medicine: Observational Studies, Electronic Health Records, Biobanks and Continuous Monitoring," *Human Molecular Genetics* 27, R1 (2018), https://doi.org/10.1093/hmg/ddy114.

[420] Frederick E. Dewey et al., "Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease," *The New England Journal of Medicine* 377, no. 3 (2017), https://doi.org/10.1056/NEJMoa1612790.

[421] Johnson et al., "Precision Medicine, AI, and the Future of Personalized Health Care."

[422] Ward et al., "Harnessing the Potential of Multiomics Studies for Precision Medicine in Infectious Disease."

[423] Naveen L. Pereira et al., "COVID-19: Understanding Inter-Individual Variability and Implications for Precision Medicine," *Mayo Clinic Proceedings* 96, no. 2 (2021), https://www.sciencedirect.com/science/article/pii/S0025619620313847.

These include associations with single-nucleotide polymorphisms (SNPs) (i.e., one base-pair changes,[424] variants in multiple alleles of a gene,[425] and epigenetic changes).[426] Various host biomarkers have been identified, which can identify individuals with a potentially poor prognosis and allow for earlier interventions.[427] While not well characterized for SARS-CoV-2 treatments, precision medicine can affect therapeutic choices.

For example, a study of the cytochrome P450 enzyme, CYP2D6, in a military population identified considerable variation in enzyme activity, which predicted variation in the metabolism of primaquine.[428] As primaquine is a standard treatment for *P. vivax* malaria, this inter-individual variability can have a significant effect on disease outcome. Knowing a warfighter's genotype could in the future assist in tailored prescription of primaquine, and better prepare combatant command leaders and medical providers for potential episodes of treatment failure due to host pharmacogenomic characteristics.[429]

D. Observations and Recommendations

The purpose of this analysis is not to provide specific recommendations on the use of, or investment in, individual diagnostic technologies, but to provide situational awareness on the current state of precision medicine. By providing insight into methods for the implementation of precision medicine concepts (with particular relevance to chemical and biological diagnostic technologies), we envision that decision-makers may be better prepared to understand the broad panoply of options available to them. Precision medicine is a rapidly advancing field, and this analysis provides a base of knowledge which can be updated as technologies advance in the future.

That being said, our analysis produced several broader observations regarding translating advances in precision medicine into military medical diagnosis. First, we highlight a few examples of how precision medicine could be implemented within the military medical system. Second, we examine the differences between civilian and military populations that make them unique for precision medicine diagnostics. The bulk of the research in the precision medicine field is

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[424] Ellinghaus et al., "Genomewide Association Study of Severe Covid-19 with Respiratory Failure."

[425] Linda Kachuri et al., "The Landscape of Host Genetic Factors Involved in Immune Response to Common Viral Infections," *medRxiv*, 2020, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273301.2/.

[426] Swati Bhat, Praveen Rishi, and Vijayta D. Chadha, "Understanding the Epigenetic Mechanisms in SARS CoV-2 Infection and Potential Therapeutic Approaches," *Virus Research* 318 (2022), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9236910/.

[427] Adam G. Laing et al., "A Dynamic COVID-19 Immune Signature Includes Associations with Poor Prognosis," *Nature Medicine* 26, no. 10 (2020), https://www.nature.com/articles/s41591-020-1038-6.

[428] Michele D. Spring et al., "Determination of Cytochrome P450 Isoenzyme 2D6 (CYP2D6) Genotypes and Pharmacogenomic Impact on Primaquine Metabolism in an Active-Duty US Military Population," *The Journal of Infectious Diseases* 220, no. 11 (2019), https://academic.oup.com/jid/article/220/11/1761/5573042#186367876.

[429] Ibid.

conducted by the civilian sector and tends to focus on pathologies that may be less relevant to active-duty military populations. In some cases, military populations may be particularly well-suited to a precision medicine approach or require different considerations than the broader U.S. population. Finally, there are some challenges and drawbacks with the implementation of precision medicine in diagnostics that we highlighted for consideration.

1. Application of precision medicine and military medical diagnosis

An intersection between precision medicine and military medical diagnosis is not without precedent, with current efforts to improve diagnosis in surgical medicine. An example program which touches on many of the technologies and approaches mentioned in this report is the Uniformed Service University's Surgical Critical Care Initiative (SC2i), which was implemented to develop clinical and biomarker-driven clinical decision support systems to improve patient outcomes in high-risk conditions.[430] SC2i is a public-private partnership between Walter Reed National Military Medical Center, Duke University, Emory University, and Grady Memorial Hospital.

The goal of the initiative was to improve patient outcomes and resource usage for patients with traumatic injuries. Clinicians collected serum, tissue biopsies, wound effluent, and urine to develop a biobank of patients recovering from traumatic injuries. Samples were then processed using a variety of molecular assays to develop cytokine, chemokine, protease, bacteriological, pathogen taxonomic, and ribonucleic transcriptomic profiles of each patient during the course of their treatment. Molecular biology data was aggregated with healthcare and personal information into a repository. Two clinical decision support systems have been developed as a result of SC2i: one to identify and treat invasive fungal infections and a second to maximize the utility of blood transfusions. Ongoing efforts are to identify panels of biomarkers to predict battle-wounded patients at risk of wound dehiscence (reopening due to improper healing).

This approach, while focused on trauma patients who have undergone surgery, may be applicable to military infectious disease patients. As a notional example, following an outbreak of an infectious disease, samples could be collected during the course of treatment from patients who recover fully with mild symptoms and compared to those who have longer term or more severe symptoms. Identification of biomarkers from these samples could inform future clinical decision support systems, treatment protocols, or procurement of materiel for patients at risk of severe symptoms (e.g., giving patients a higher dose of antibiotic or a longer course, allocating resources such as ventilators for patients more likely to need them, transporting higher-risk patients to a higher role of care).

[430] Arnaud Belard et al., "The Uniformed Services University's Surgical Critical Care Initiative (SC2i): Bringing Precision Medicine to the Critically Ill," *Military Medicine* 183, suppl_1 (2018), https://pubmed.ncbi.nlm.nih.gov/29635571/.

Additionally, different precision medicine technologies may be more or less relevant depending upon the level of care a treatment facility can provide. For example, paper-based diagnostics that can be used in far-forward Role 1 or Role 2 medical treatment facilities could be used to inform triage or medical transport decisions. Precision medicine technologies requiring extensive, specialized equipment (e.g., proteomics, transcriptomics, or medical image analysis) would likely be implemented at higher levels of care in Role 3 or Role 4 medical treatment facilities. Understanding where a patient is likely to be treated can help to guide investments in diagnostic devices, as developed technologies should be usable at the role of care where patients are typically treated for those diseases.

Overall, precision medicine seems more likely to change the manner in which diagnostic technologies are employed, rather than dramatically shifting the field of diagnostics itself. The majority of studies reported in this paper describe improved clinical outcomes from precision medicine due to adjustments in their *treatment* as opposed to adjustments in their *diagnosis*. There are a few exceptions to this rule, including nanomaterials, digital PCR, CRISPR-based systems, AI/ML, and ELISA, which may allow for disease diagnosis at lower levels of care or earlier during the course of an infection. Integrating CBRN agent biomarkers into previously developed precision medicine technologies would be one way to capitalize on advances in this field, but it would require the identification of relevant biomarkers.

2. Precision medicine in a military population

Precision medicine approaches can be applied to both civilian and military populations, but there are a few factors in which these two communities differ that could affect implementation. First, the diseases of concern to the military population differs from that of the civilian population. Many civilian precision medicine technologies focus on the identification and treatment of cancer and diseases associated with old age, whereas the relatively young and healthy military population may be more concerned with traumatic injuries and/or CBRN agent exposure.

As seen in Table 9, few of the CBRN agents of concern have genome-wide association study data. Partnering with civilian research organizations to develop precision medicine technologies and approaches for diseases and agents of concern to the military population may be one way forward. Second, some precision medicine approaches may be particularly suited toward a military population. For example, the DoD already collects lifestyle information on their military population that could be useful for personomics. Additionally, the DoD could standardize collection of personomic data much more readily than the disjointed civilian medical care system.

3. Challenges using precision medicine in diagnostics

Precision medicine has advanced significantly in the past years, but several challenges remain in the field as a whole and in relation to diagnostics. These include overdiagnosis, time and cost, and large datasets.

a. Overdiagnosis

Overdiagnosis is defined by the National Cancer Institute as "finding cases of [disease] with a screening test that will never cause any symptoms."[431] It can trigger medically unnecessary treatment, resulting in both increased costs and harm to the patient.[432] Increased testing for biomarkers has been shown to increase diagnosis of disease without improving mortality rates in several specific cases.[433] Ensuring new precision medicine approaches actually result in improved patient outcomes should be a necessary step of programmatic evaluation to avoid overdiagnosis.

b. Time and cost

Currently, many precision medicine technologies may not be timely enough to influence clinical decision-making or affordable enough for widespread use, particularly in far-forward environments. As technologies improve, both the time to run samples and cost of diagnostic tests will likely decrease. Precision medicine could have benefits in many specific diagnostic applications, but may not always be beneficial. A cost-benefit analysis of precision medicine-based diagnostic technologies over current gold-standard procedures should be considered before investment in any specific systems are made.

c. Large datasets

Development of the biomarker associations necessary for precision medicine requires a large and diverse amount of data, which presents its own challenges, including data collection, storage, and security. The diversity of a population represented in a biological dataset is of paramount importance when developing associations between biomarkers and disease or clinical outcomes. As mentioned previously, different subpopulations of individuals may not exhibit the same biomarkers in response to the same diseases or treatments. Undersampling of minority subpopulations during sample collection should be avoided for effective precision medicine approaches.

Additionally, the datasets employed for precision medicine initiatives can become massive in scale. For example, in the SC2i program, an average of 30 samples are collected per patient across multiple visits.[434] These samples can result in over 30,000 clinical and biomarker data points per individual per visit, with digital memory of this dataset entering the petabyte range. SC2i has

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[431] "NCI Dictionary of Cancer Terms: Overdiagnosis," National Cancer Institute Website, accessed November 30, 2022, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overdiagnosis.

[432] John Brodersen et al., "Overdiagnosis: What It Is and What It Isn't," *BMJ Evidence-Based Medicine* 23, no. 1 (2018), https://doi.org/10.1136/ebmed-2017-110886.

[433] Ibid.

[434] Belard et al., "The Uniformed Services University's Surgical Critical Care Initiative (SC2i): Bringing Precision Medicine to the Critically Ill."

attempted to address this scale by using cloud-based computing, but consideration of the security risks associated with cloud-based computing of military biological data is crucial.

Biological data could be misused either indirectly (e.g., personal identification of warfighters, environmental targeting of troops) or directly (e.g., directed development of engineered bioagents).[435] Possible national security implications should be considered by decision makers when implementing precision medicine concepts into military medical diagnostics.

[435] Diane DiEuliis and James Giordano, "Balancing Act: Precision Medicine and National Security," *Military Medicine* 187, Suppl 1 (2021), https://academic.oup.com/milmed/article/187/Supplement_1/32/6489948.

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Appendix C. Abbreviations

AI	artificial intelligence
ASSURED	affordable, sensitive, specific, user-friendly, rapid, equipment-free, delivered
AUC	area under curve
CAR	chimeric antigen receptor
CB	chemical and biological
CBRN	chemical biological radiological nuclear
CDC	Center for Disease Control
CE	capillary electrophoresis
CE-MS	capillary electrophoresis mass spectroscopy
CFTR	cystic fibrosis transmembrane conductance regulator
COVID-19	coronavirus disease 2019
CRE	carbapenem-resistant *Enterobacteriaceae*
CRISPR	clustered regularly interspaced short palindromic repeats
CT	computerized tomography
CYP	cytochrome P450
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
DST	drug sensitivity testing
DTRA	Defense Threat Reduction Agency
EBI	European Bioinformatics Institute
EBOV	Ebola virus
EGFR	epidermal growth factor receptor
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EVD	Ebola virus disease
FDA	Food and Drug Administration
FIA	flow injection analysis
FRET	fluorescence resonance energy transfer
G6Pd	glucose-6-phosphate deficiency
GM-CSF	granulocyte macrophage colony stimulating factor

GWAS	genome wide association study
HDL	high-density lipoprotein
HITS-CLIP	high throughput sequencing of RNA isolated by cross linking immunoprecipitation
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPLC	high performance liquid chromatography
HPV	human papilloma virus
HR-MAS-NMR	high-resolution magic angle spinning nuclear magnetic resonance spectroscopy
IBD	inflammatory bowel disease
IBM	International Business Machines
IBS	irritable bowel syndrome
ICU	intensive care unit
ID	infectious disease
IDA	Institute for Defense Analyses
IFN	interferon
IL1	interleukin-1
IL17A	interleukin-17A
IL6	interleukin-6
IL8	interleukin-8
INF	interferon
ISG	interferon-stimulated genes
KIR	killer immunoglobulin-like receptor
LASV	Lassa virus
LC-MS	liquid chromatography-mass spectrometry
LDL	low density lipoprotein
LOD	limit of detection
MALDI	matrix-assisted laser desorption/ionization
MARV	Marburg virus
MIC	minimum inhibitory concentration
ML	machine learning
MRNA	messenger ribonucleic acid
MS	mass spectrometry
MSMD	mendelian susceptibility to mycobacterial disease
MTF	medical treatment facility

NAAT	nucleic acid antigen test
NATO	North Atlantic Treaty Organization
NCI	National Cancer Institute
NGS	next-generation sequencing
NHGRI	National Human Genome Research Institute
NHP	non-human primates
NIH	National Institutes of Health
NMR	nuclear magnetic resonance
NPS	neutrophilic suppressive
OP	organophosphate
PCAST	President's Council of Advisors on Science and Technology
PCR	polymerase chain reaction
PCT	procalcitonin
PM	precision medicine
ProADM	pro-adrenomedullin
QD	quantum dot
qPCR	quantitative polymerase chain reaction
R&D	Research and Development
RNA	ribonucleic acid
RPA	recombinase polymerase amplification
RT	reverse transcriptase
RUO	research use only
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBS	sequencing-by-synthesis
SHERLOCK	specific high-sensitivity enzymatic reporter unlocking
SMRT	single molecule real-time
SNP	single nucleotide polymorphism
SPR	surface plasmon resonance
SUDV	Sudan ebolavirus
TB	tuberculosis
TDM	therapeutic dose monitoring
TNF	tumor necrosis factor
TOF	time of flight
UK	United Kingdom

US	United States
USD	United States Dollars
UV	ultraviolet
WGS	whole genome sequencing
WHO	World Health Organization
WMD	weapons of mass destruction
ZMW	zero-mode waveguides

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14. ABSTRACT

As per the 2008 President's Council of Advisors on Science and Technology, precision medicine is "The tailoring of medical treatment to the individual characteristics of each patient…to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment." Precision medicine concepts could be implemented with chemical and biological (CB) diagnostic technologies to enhance medical decision-making. A literature review was performed to identify recent advancements made in precision medicine. The focus was on CB diagnostics, which identified various precision medicine concepts, technologies, and products on the market to assess the state of precision medicine. While it was found that there is a lack of research directly tying precision medicine, diagnostics, and CB agents, there are multiple avenues identified in which precision medicine can assist when dealing with CB agents, not necessarily enhancing diagnoses but improving clinical outcomes. The information in this analysis highlights the need for technology acquisitions and creation of large datasets to implement precision medicine concepts.

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