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Opportunities, Resources, and Techniques for Implementing Genomics in Clinical Care

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Summary

Dramatic advances in technologies for assessing genomic variation and understanding the influence of genomic variants on health and disease are propelling the transition of genomics from the research laboratory into clinical care. "Genomic medicine," or the use of genomic information about an individual as part of their clinical care, is increasingly gaining acceptance in routine practice, including using genomics for assessing disease risk in individuals and their families, diagnosing rare and undiagnosed diseases, and improving drug safety and efficacy. Here we describe the major concepts and measures of genomic variation currently of clinical importance,

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discuss approaches to interpreting genomic sequence variants, identify publicly available tools and resources for genomic test interpretation, and address several key barriers in using genomic information in routine clinical practice.

Introduction

Increased understanding of the role of genomic variants in human health and disease, coupled with improved technologies for measuring and interpreting these variants, is enabling the integration of genomics into clinical care. This covers a spectrum of research and implementation efforts, including *discovery research* to assess genotype-phenotype associations, *clinical validation* to assess clinical outcomes after using genomic information to direct therapy or mitigate disease risk, and *clinical implementation* to develop processes for performing genomic testing and using the results in clinical care (Table 1). Clinical validation and implementation in particular are considered by the National Human Genome Research Institute (NHGRI) to comprise “genomic medicine,” which it defines as using genomic information about an individual as part of their clinical care [1]. A widening array of such applications is gaining acceptance in routine care, including using genomics for assessing disease risk [2,3], diagnosing rare and undiagnosed diseases [4,5], and improving drug safety and efficacy [6,7].

Challenges in genomic medicine implementation have been widely discussed [1,8–10] and include lack of familiarity and understanding among both clinicians and patients, limited access to genomic expertise and testing, limited reimbursement for genomic medicine activities, and lack of infrastructure to support the informatics demands of integrating genomic information into electronic medical records (EMRs) and the clinical workflow (Box 1). Several efforts in the U.S. and abroad are successfully bridging these gaps [11–15], most notably in the U.K.’s 100,000 Genomes project [14] which is bringing whole genome sequencing directly into clinical care. As genomic medicine technologies and methods become increasingly accessible, clinicians will need to understand and adapt them in ways that make sense for their unique practice settings.

This paper is the first in a five-part series designed to introduce practicing clinicians to the opportunities and challenges of genomic medicine implementation. In this first paper, we lay the groundwork for understanding the technologies, terminologies, advantages, and disadvantages of the emerging implementation approaches described in four subsequent papers on assessing disease risk, diagnosing rare and undiagnosed diseases, improving drug safety and efficacy, and assessing outcomes of implementation. Note that use of tumor genomic sequence variants for targeted chemotherapy and informing eligibility for clinical trials [16] and genome sequencing for identification and sensitivity testing of infectious agents [17] have been in clinical practice for several years and will not be addressed in this or subsequent papers in this series. We will, however, describe the major technologies used in genomic medicine, discuss approaches to interpreting genomic sequence variants, identify publicly available tools and resources for genomic test interpretation, and address several key barriers to using genomic information in routine practice.

Critical technologies in genomic medicine

Family health history

While molecular techniques for assaying human genomic variation have become increasingly sophisticated and available since the launch of the Human Genome Project in 1990, the value of a careful family health history has been recognized since the time of Hippocrates [18]. Still one of the simplest, cheapest, and most predictive genomic tests, family health history information is rarely available in medical records aside perhaps from a cursory mention such as “father died age 61, stroke,” and is rarely if ever represented as structured data that can be easily retrieved computationally. Yet a family history of early coronary disease or cancer, especially among multiple relatives, often confers an increased risk many times greater than that conferred by the majority of identified genomic variants [19,20]. Several user-friendly, patient-facing family history tools are available [21,22] and have been shown to be powerful identifiers of increased risk for a variety of serious diseases [3,20]. Though devoid of the seductive, high-tech nature of other genomic technologies, patient-entered family history provides essentially a “bioassay” of the effect of a patient’s genomic variants in the other persons most likely to carry them—their biologic relatives. It also captures the effect of shared environmental exposures, is relatively easy and inexpensive to collect, and has demonstrated reliability [23]. It is discussed at length in the second paper in this series.

Clinically important genomic variation

Before discussing technologies for assessing genomic variation it may be useful to identify the types of genome sequence variants that are most clinically important to assess. At present these largely comprise two types (Box 2). First and most widely described are changes in the exons, or coding regions of genes, that render the gene’s protein product(s) inactive (commonly called “loss of function,” or “LoF”) or aberrantly active (often called “gain of function” or “GoF”). LoF variants are typically missense or nonsense variants (two of the types of single base-pair sequence changes often referred to as “single nucleotide polymorphisms,” or “SNPs”) that inactivate or impair the function of the gene’s protein product, such as the adenine to thymine transversion in the codon for amino acid 6 of the hemoglobin B gene that results in sickle hemoglobin. While the vast majority of DNA variants are SNPs, variants can also be insertions or deletions of 1 or 2 base pairs resulting in a “frameshift” that prematurely terminates the protein product, or a single-base change at a splice site that impairs correct assembly of the messenger RNA to code that protein. Larger deletions, sometimes thousands or even millions of base pairs in length, can also be important clinically if they remove a chromosomal region needed for normal function, as in the chromosome 22q11.2 deletion that produces distinctive phenotypes such as DiGeorge and velocardiofacial syndromes [24]. Larger insertions can introduce an extra copy of a gene whose protein product (often an enzyme) may increase drug metabolism, yielding sub-therapeutic drug levels or toxic drug effects, as with duplications of the gene *CYP2D6* that is involved in the metabolism of many commonly used medications [25].

The second type of genomic variation involves changes in the other 98% of the human genome comprising the non-coding sequence. Key functional elements in non-coding DNA

include promoters, enhancers, transcription factor binding sites, and non-coding RNAs, all of which may influence the amount of gene product produced. Though technically not part of the DNA sequence, epigenetic changes to the nucleotides themselves or their associated proteins (such as methylation of cytosine residues or variation in the histone proteins that package DNA into chromosomes) can affect the accessibility of DNA segments to be transcribed and reduce or eliminate their transcription altogether. The relevance of these types of non-coding variants to clinical care is only beginning to be understood and for the most part will not be addressed in this series.

SNP array genotyping

Commonly used SNP arrays rely on haplotypes, or segments of DNA that have been inherited from a common ancestor without recombination, whose sequence has been defined through haplotype mapping efforts [26]. Identifying a single SNP in a haplotype region often allows the surrounding sequence to be inferred with great accuracy. Such “tag SNPs” are found throughout the human genome in both coding and non-coding regions, and have been combined into large-scale arrays (“SNP arrays”) that assay for the presence of hundreds of thousands or even millions of genomic variants. In addition to directly interrogating SNPs, the availability of reference sequence databases has enabled accurate imputation of common sequence variation, or variants present in about 1–5% of a population. Imputation is a mathematical technique that calculates the probability of a specific base at an unmeasured genomic location based on previously estimated relationships with neighboring measured variants. Imputation is most accurate when the sequences surrounding these known variants are well-characterized. Unfortunately, this is truer for some populations than others, with sequence information in populations of non-European ancestry being notably less complete [27].

First introduced for research use in 2005, genome-wide SNP arrays have been the foundation for the thousands of genome-wide association studies (GWAS) that have identified tag SNPs associated with innumerable diseases and traits and led to many critical discoveries about the role of genomic variation in health and disease [28]. Since that time, arrays have moved into clinical use and are largely replacing karyotyping for detection of aneuploidies and large chromosomal aberrations, and have been combined into panels for assessing variants in genes involved in drug response (often called “pharmacogenes,” the subject of the fourth paper in this series) and in risk of common diseases. SNP arrays have also been the basis for direct-to-consumer tests for predicting disease risk or assessing ancestry that are becoming increasingly available and popular. SNP arrays remain the most economical means for characterizing common (and with imputation, somewhat rarer) variants in an individual’s genome, particularly if that person is of European ancestry. Efforts are underway to improve the representation of variants from non-European ancestry populations on SNP arrays [27].

Genome sequencing

Despite their many strengths, SNP arrays have several weaknesses that may limit their value in individual patients, particularly when the genomic variation underlying a patient’s condition is believed to be rare. SNP arrays assess only known (that is, previously identified)

SNPs, typically those that are present in sizeable numbers across a population, rather than variants that may be rare or even unique to an individual. They also rely on accurate reference databases for imputing the surrounding variants not directly assayed by the array, and are thus less precise for examining certain genomic regions, such as highly-repetitive DNA, that are technically difficult to assay. Arrays are also typically inadequate for assessing most types of structural variation, unless the structural variant happens to be frequently associated with a common tag SNP, and as noted above they are currently heavily biased toward European ancestry content.

Genome sequencing transcends many of these barriers by performing a base-by-base read-out of (theoretically) every nucleotide in the genome. “Theoretically” because there are still chromosomal regions that are technically difficult to sequence reliably, particularly highly repetitive regions and areas of high guanine/cytosine (GC) content, though technologies continue to improve [29]. Sequencing methods are continually evolving and a review of them is outside the scope of this paper; authoritative reviews are available [30,31]. Understanding these technologies is not critical to understanding their clinical applications, though the ordering provider does need to understand the strengths and weaknesses of a given test to ensure it is appropriate to their indication for testing. This is best ascertained in consultation with a molecular pathologist proficient in genomic analysis or in discussions with the laboratory likely to perform the test.

Four main types of DNA sequencing approaches are used clinically, focusing on single genes or targeted gene panels, or extending to the entire exome (the protein-coding regions comprising 2% of the human genome) or genome, with increasing proportions of the genome sequenced in each (Table 2, [32]). Single gene assays and targeted gene panels are largely used when one gene or a small group of genes are strongly implicated by a patient’s clinical characteristics, while exome and genome sequencing are used when clinical characteristics do not clearly point to one gene or group of genes, and/or other methods have failed to identify a causative variant. Genome sequencing has the added advantage over exome sequencing of providing more even coverage across the genome. It thus avoids the potential for differential amplification of difficult-to-sequence genomic segments and preferential capture of reference alleles (rather than alternative alleles) compared to targeted methods [29,33]. Other advantages of genome over exome sequencing methods include better resolution of structural variants such as insertions and deletions and a faster generation of sequence data [5], though genome sequencing methods produce substantially more data needing interpretation. Their biggest disadvantage is their higher cost. Interpretation of both exome and genome sequencing is facilitated by “trio” sequencing not only of the index patient but of both his/her parents, allowing rapid identification of *de novo* variants arising during gametogenesis and embryogenesis in the child [34]. A complementary high-throughput sequencing method, RNAseq, quantifies RNA transcripts to assess gene expression and is showing promise in detecting non-coding variants in cancer and neuromuscular diseases [35–37], but at present is less available clinically.

Choices among these methods are somewhat driven by costs and reimbursement policies, though prices quoted for single-gene and gene-panel sequencing can often approach or exceed the more comprehensive methods (exome and genome sequencing), which are

themselves continually declining in cost. Choices may also be influenced by the informatics capabilities of the sequencing laboratory since exome and genome sequence analyses are computationally intensive, with significant informatics and data storage costs. A simultaneous strength and weakness of the two comprehensive methods is the massive amount of genomic variant information they produce, as each of us carries 4–5 million variants, tens or hundreds of thousands of which are rare (frequency of < 0.5%). Sorting through and interpreting variants that have been seen rarely or possibly never before, and whose clinical relevance is unknown, is a formidable informatics challenge and one that requires continuous updating and reinterpretation as understanding of sequence variants increases. Sharing of data on variants and their phenotypic associations among clinicians and researchers is critical to improving variant interpretation because the more times a variant is reported and the better the phenotype(s) associated with it are defined, the firmer the classification will be. This is especially true for variant data from ancestrally diverse populations, since if a variant is rare in one ancestry but common in another, it is unlikely to cause an uncommon disease [38]. For these reasons, laboratories, clinicians, and patients are strongly urged to deposit their sequence information into large-scale, de-identified, publicly available data resources such as those described below to improve the quality of genome interpretation for everyone.

Genomic variant interpretation and actionability

Assessing pathogenicity of variants

As noted above, sequencing part or all of an individual's genome can produce as many as several million variants in which that person differs from the reference sequence; thousands of these variants have scant or no available information in current databases [39,40]. Determining which of these variants may cause a particular phenotype, or may put the person at risk for future serious illness or adverse drug response, is a painstaking process. First, the quality and validity of the generated sequence data and the identified variants must be carefully assured [41]. This is typically followed by filtering out variants unlikely to cause disease, often because they occur at a frequency much higher than the population frequency of the disease or phenotype under consideration [41]. Further interpretation typically follows a series of professional guidelines such as those published in 2015 by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology [42], and seeks to divide variants into those that are clearly disease-causing ("pathogenic," or "P"), clearly non-disease-causing ("benign," or "B"), or whose relationship to disease is unknown ("variants of unknown significance," or "VUS"). If the pathogenicity of a variant is not certain, often because it has not been seen before, but is still strongly implicated because it is believed to have the same effect on gene function as a variant previously classified as pathogenic, it is classified as "likely pathogenic," or "LP," and similarly for variants that are "likely benign," or "LB" (Table 3).

This five-tiered classification scheme has been arrived at using data from a wide variety of sources (population data, functional data, *in silico* functional predictors, segregation data, etc.) that were then combined using a series of scoring rules to assign points in a complex but systematic way [42]. It should be noted that the ACMG guidelines on variant

interpretation are not intended for the interpretation of variants found only in specific tissues or in tumors (often called “somatic variants,” as opposed to “germline” or inherited variants found in every cell of the body). Nor do they apply to pharmacogenomic variants, which are interpreted in the context of clinical prescribing guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [43].

The large intermediate class of VUS is particularly problematic because their clinical relevance is truly unknown, even when occurring in a known disease-causing gene such as *BRCA1* (causing hereditary breast and ovarian cancer) or *COL3A1* (causing vascular Ehlers-Danlos syndrome). It is important to remember that each individual carries millions of variants, many by chance falling within such disease genes (especially if those genes are large). When variants are detected in a patient with a phenotype presumably related to that gene, VUS can be misinterpreted as indicating the need for sometimes drastic therapeutic actions when none should be taken. Such variants can, however, be very important to be aware of if subsequent information becomes available that shifts them into the P/LP classification, a situation that is increasingly arising as knowledge about genomic variation increases [44,45]. Shifts can also occur between more definitive classifications, such as benign/likely benign to P/LP and vice versa, sometimes with significant implications for clinical management, though such changes to date have been infrequent [44]. They may become more common as data accrue. While consensus has yet to emerge on the appropriate frequency and intensity with which re-interpretation should be pursued and what evidence is the most informative, there is consensus that reclassification in light of new biologic knowledge or changing clinical circumstances is appropriate, and it presents a real challenge for clinicians and patients trying to act upon sometimes changing genomic variant information [45,46].

Most U.S. laboratories now report gene variants classified as pathogenic or likely pathogenic (P/LP) in a gene likely to be responsible for a patient’s clinical characteristics as “primary” findings (that is, findings related to the indication for testing). Because they are often looking at large segments of the genome, however, they also identify P/LP variants in other genes unrelated to the indication for sequencing that may be strongly predictive of risk of other diseases. The ACMG has identified 59 such genes, in which P/LP variants are believed to be strongly associated with potentially life-threatening conditions such as cancer, cardiac arrhythmias, and cardiomyopathy, and for which changes in treatment or frequency of surveillance are recognized to be beneficial [47]. Many laboratories feel compelled to report these “secondary findings” as recommended by ACMG guidelines, while recognizing that not all such variants cause disease in every patient, a characteristic referred to as “variable penetrance” (ghr.nlm.nih.gov). The ACMG and other expert bodies, however, specifically recommend *against* returning VUS (as opposed to LP/P variants) as secondary findings for the very reasons detailed above [47].

Actionability of variants

Most laboratories, clinicians, and patients agree that secondary findings should be reported back to patients who consent to receive this information, and to their clinicians, if there is effective clinical action to be taken. What clinical actions are considered effective is, of

course, a subjective matter, as what might be deemed acceptable and effective in one clinician-patient scenario might be quite unacceptable to another. This question of "actionability" involves considerable contextual information and clinical judgement, since what might be reasonable clinical action to consider in persons contemplating starting a family, for example, vs. elderly persons with terminal disease vs. ostensibly healthy young children, could differ dramatically. Actionability and reporting in children in particular remain topics of intense interest and debate [48,49], though several secondary findings may be relevant to the management of children such as genes related to familial hypercholesterolemia, cardiomyopathy, early onset cancers, and cardiac arrhythmias. Personal choices may also vary considerably, with some individuals wanting to receive all variant information with any possible "personal utility" in making, say, lifestyle choices, and others preferring not to receive any information at all [50]. Standards for actionability have been developed and published by the NHGRIfunded Clinical Genome (ClinGen) Resource [51] that grade characteristics such as severity of the condition associated with the variant, likelihood that disease will develop in variant carriers, effectiveness of available interventions, and nature (or invasiveness) of the available interventions, all in the context of the strength of available evidence for these four characteristics. While personal choices will still vary, this at least provides a framework for discussing what results patients are willing to receive and how those wishes may change over time.

Return of genomic research results

The processes and impacts of returning genomic results (especially those derived from research studies) to patients and clinicians have been the subject of nearly as much research as the actionability of the variants themselves. Considerable debate continues on what information should be returned to whom, by whom, how, and when [52,53]. These issues can be particularly fraught when children or infants are involved [54,55] and extend to ethical concerns such as the "duty to warn" first-degree relatives of persons carrying P/LP variants for serious and preventable illnesses (who themselves have a roughly 50% chance of also carrying those variants), balanced against the right of a patient or research participant to privacy and confidentiality. Consensus seems to be growing, however, that patients have a right to receive genomic information with clear implications for their health, and a right to refuse that information; that such results should be derived from clinically validated and certified processes; and that counseling on the potential implications of these findings should be provided both before patients agree to undergo testing and after they receive the results [56,57]. Once a P/LP variant is identified in an individual, family members can be screened for it and should they consider being tested, each should also receive genetic counseling. Although many concerns have been raised about the potential adverse impact of receiving genetic results [57], often stemming from early negative experience with severe and irreversible monogenic conditions, communicating genetic risks of disease has largely not been shown to affect risk-reducing behaviors or produce depression and anxiety [58,59]. This will remain an active area of research as the quantity and quality of returned genomic information continues to evolve.

Genomic resources and genomic medicine studies

Genomic resources

A broad array of genomic medicine constituencies, from the very large numbers of patients and their families to progressively smaller numbers of clinicians, geneticists, laboratory scientists, and genomics researchers, requires a similarly broad array of resources for clinical reference, education, and data sharing (Table 4). Such resources are steadily increasing in both number and usefulness. A few representative examples are described below.

First-line clinical references are critical for recently diagnosed patients and their families. For example, the Genetics Home Reference (GHR) of the National Library of Medicine (NLM) provides consumer-friendly, basic information on health conditions with a genetic basis. Clinicians who are not genetics specialists are also in need of ready information on the medical effects of genomic variants, which can be found in NLM's MedGen. Clinicians may also be seeking available genomic/genetic tests and testing laboratories, for which NLM's Genetic Testing Registry (GTR) is a valuable resource. Pharmacogenomic information on variants related to drug selection and dosing are available to them through the CPIC website. More advanced clinicians and genetics specialists, including genetic counselors, are likely to search Online Mendelian Inheritance in Man (OMIM), while laboratories and clinicians may refer to NLM's ClinVar, a public archive of reported variants, associated clinical characteristics, and pathogenicity interpretations. Consensus interpretations of the clinical actionability of variants builds upon information in ClinVar and is available in ClinGen. Genomics researchers use highly complex and integrated annotation and aggregation resources such as GeneCards for information on gene structure and function for all annotated and predicted human genes, as well as more specialized resources such as the Pharmacogenomics Knowledge Base (PharmGKB) and The Cancer Genome Atlas (TCGA) for subsets of genes related to drug response and cancer, respectively. The "BRCA Exchange" data resource for *BRCA* variant interpretation [60] provides a novel approach to aggregating data for real-time variant classification and even includes a simplified interface through a mobile app to search the database and request notifications of updates on specific variants. Many other genomic databases are available but a summary of them is beyond the scope of this paper; an excellent online compilation with descriptions and links is available from the Human Genome Variation Society at http://www.hgvs.org/locus-specific-mutation-databases.

Educational resources are also in considerable demand, particularly for patients and non-geneticist clinicians, who can access the NHGRI Talking Glossary, the Wellcome Trust's Your Genome, the NHGRI Genetics/Genomics Competency Center (G2C2), and the University of Washington/NCBI Bookshelf GeneReviews. Data sharing has also been critical to determining the functionality of variants and identifying the clinical characteristics associated with disease-causing variants, and several data sharing resources are available including ClinGen's GenomeConnect and MyGene2 of NHGRI's Centers for Mendelian Genomics. These sites allow patients to deposit their own genomic data and clinical characteristics for open public sharing in hopes that their information may be useful to other

patients, clinicians, and researchers. Clinicians (typically geneticists) encountering an undiagnosed patient with a novel genomic variant often need just a single additional case with a P/LP variant in the same gene and similar clinical characteristics to identify the causative gene; they can seek such patients through resources such as the Matchmaker Exchange. This can be especially useful for managing genomic information in patients with undiagnosed diseases, the subject of the third paper in this series.

Laboratories are contributing to growing community resources such as NLM's ClinVar. They can also use compiled resources such as the Genome Aggregation Database (gnomAD) to determine whether a variant has previously been detected and if so, at what frequency across ancestries. By ACMG interpretation rules variants will be classified as benign if they are too common in a population to be causing a rare disease [42]. Researchers can also consult specific data resources such as the Gene-Tissue Expression (GTEx) database describing gene expression and its genetic determinants across over 50 human tissue types, or the Monarch and Alliance of Genome Resources initiatives that relate human phenotypes and diseases to those in a variety of model organisms for further study.

Genomic medicine studies

Several major genomic medicine implementation efforts are ongoing in the U.S. and abroad and have recently been reviewed [61]. Two such studies, each performing genome sequencing in 100,000 or more patients and using the results in clinical care, include the Geisinger MyCode Project (https://www.geisinger.org/mycode) in partnership with Regeneron Pharmaceuticals, and the Genomics England 100,000 Genomes Project in collaboration with England's National Health Service (https://www.genomicsengland.co.uk/). The latter has recently been expanded to 5,000,000 genomes. Similar projects in other medical systems and even other countries are likely to be initiated soon.

Building on its 2011 strategic plan [62], NHGRI has moved quickly to extend existing research programs into genomic medicine implementation and to develop others to fill critical gaps (Table 5). These programs can be viewed along a continuum from those highly focused on in-depth characterization of and interaction with individual patients and their clinicians, such as the Undiagnosed Diseases Network (UDN) and the Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Consortium, to programs addressing broader implementation and system-wide research questions such as the Electronic Medical Records and Genomics (eMERGE) Network and the Implementation of Genomics in Practice (IGNITE) Network. Underpinning them all are critical infrastructure programs for knowledge synthesis and integration, such as the ClinGen Resource described above, as well as investigator-initiated grants and training programs. Funding for genomic medicine research programs from NHGRI and collaborating NIH Institutes is expected to total at least $775 million across fiscal years 2007 through 2022, inclusive.

A major emphasis of NHGRI studies is to develop tools and best practices for genomic medicine implementation and make them widely available for the research and clinical communities. The Clinical Sequencing Evidence-Generating Research (CSER) consortium's website (https://cser-consortium.org/), for example, contains a wide array of patient

education materials and protocol resources. The eMERGE investigators have also developed several useful tools such as the Phenotype Knowledge Base (https://phekb.org/) of validated electronic phenotyping algorithms and the Clinical Decision Support Knowledge Base (https://cdskb.org/) of practical, implemented clinical decision support (CDS) rules. The SPARK Toolbox (https://ignite-genomics.org/spark-toolbox/) of the IGNITE Network provides resources for specific interventions (such as *APOL1* [63] testing for risk of kidney disease or family history collection [3]) including educational materials, laboratory procedures, implementation guides, and clinical workflows. Assessing outcomes of genomic medicine interventions is crucial for determining their ultimate value and best practices for their use; outcome assessment is explored in detail in the fifth paper in this series.

Other considerations

Similar to many areas of clinical care, a number of medical fields and allied personnel must work together for genomic medicine to be implemented effectively. These include informaticians who are critical to the integration of genomic information into the EMR, as well as to the implementation of effective electronic phenotyping algorithms and clinical decision support [64]. While pharmacists are essential to any effective application of medical therapeutics, they are particularly valuable in interpreting pharmacogenetic variants and their impact on drug response [65]. Unique to genomic medicine is the role of the genetic counselor, a discipline that has evolved in the past 50 years "…to interpret genetic test results, and to guide and support patients seeking more information" about how inherited conditions may affect them and the risks and benefits of specific genetic tests [66]. Genetic counselors play a key role in helping patients understand indications for and potential implications of genetic and genomic testing for themselves and their families [67]. Until recently they worked almost exclusively in partnership with medical geneticists, but as the use of genomic information has spread to more common, complex diseases, the need for genetic counselors and for more streamlined models of providing information to patients outside the realm of monogenic disorders has grown considerably. Genetic counselors are also playing an increasing role in variant interpretation and with laboratories and payers to optimize utilization of genetic tests [68].

Multidisciplinary approaches are essential to address some key challenges in using genomic information in clinical care, such as ensuring confidentiality and avoiding or minimizing the potential for genetic discrimination [69]. Critical to all genetic testing and return of results is proper informed consent and adequate genetic counseling on the potential benefits and risks of testing. Such risks include discovering unmodifiable risk of severe disability or early mortality, unsuspected familial relationships, significant risks to potential offspring that may affect reproductive decision-making, or finding nothing at all to explain a patient's condition. The rapid evolution in understanding genomic variation and the dynamic nature of variant interpretation will continue to pose challenges for clinicians, laboratories, and patients in appropriately applying this information to clinical care. An easily overlooked aspect of genomic medicine is the long-term management of patients with important genomic findings such as an LP/P variant in an actionable gene. Primary care physicians are often left responsible for these patients' management, which can be far from simple in terms of time and complexity. The broader adoption of genomics into clinical care will only

increase this challenge. Training of the entire medical team will be required, including nurses, pharmacists, and administrative staff. Because genomic variants found in one patient may have profound implications for their family members, effective approaches are needed for surmounting intra-family communication barriers and facilitating testing of at-risk relatives ("cascade testing") [70]. Payers will need to understand and pay for these time-intensive, critical services for genomic medicine to be adopted and implemented effectively. Public health policy-makers will need to consider the appropriate role for genetic testing beyond its current use in newborn screening, which is actually largely done using enzymatic rather than genetic tests. Population-wide screening has been suggested for certain modifiable risks (hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia [71]) but has yet to be widely adopted. At present testing for these conditions remains focused largely on patients at risk, often identified through strong family histories, but indications may broaden as experience accrues [72]. Other challenges in genomic medicine implementation include navigating hurdles to reimbursement, convincing clinicians to act on genomic information, and maintaining patient privacy while sharing data in effective ways to improve variant interpretation [1]. Expanded efforts are also needed in evidence generation, encouraging data sharing and infrastructure support, improving the regulatory environment, and engaging patients and the public [73].

Conclusions

Genomic technologies and understanding of genomic variants are continuing to move from the research setting to clinical care in largely incremental steps that should be viewed as more of an evolution than a revolution. As potential clinical applications of genomic research arise, there is a strong need for dissemination and implementation research into the best strategies to promote rapid adoption, scale-up and sustained integration of these applications into routine clinical care with the aim of improving patient outcomes [74]. Equally compelling is the need for dissemination research to understand how best to spread and sustain knowledge and use of effective interventions. NHGRI collaborates with the NIH Dissemination and Implementation program (https://prevention.nih.gov/research-priorities/dissemination-implementation) to fund innovative research on dissemination and implementation of genomic medicine. Efforts to capture the growing clinical experience with genomic applications as medical centers and healthcare systems increasingly adopt them will be most effective in assessing real-world benefits and shortcomings of these approaches.

Numerous resources and materials are available to assist clinicians and patients in adopting these approaches, but accessing and sifting through them can be a daunting task. At present the best resources for clinicians may be a local geneticist or genetic counselor, perhaps locatable through the ACMG or the National Society of Genetic Counselors, or a nearby genomics laboratory or molecular pathologist identifiable through the College of American Pathology or the Association for Molecular Pathology. Telemedicine approaches may also meet the growing needs of genomic medicine [75]. Patients are also becoming increasingly sophisticated in the use of knowledge resources, and patient support and advocacy groups such as the Genetic Alliance have been effective in helping link patients with needed clinical care. Additional training and certification may be desirable to develop consulting genomic

medicine subspecialists in various medical disciplines, such as pharmacogeneticists, “genomic cardiologists” with expertise in cardiac arrhythmias and cardiomyopathies, and oncologists with expertise in cancer genomics. Even for the non-specialist practitioner, however, it seems clear that the adoption and usefulness of genomic information will continue to grow. Concomitant growth in clinicians’ familiarity and understanding of genomic medicine will be needed, as is the object of this series of papers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1. Challenges in implementation of genomic medicine [1]

- Lack of familiarity and understanding by patients and clinicians
- Limited access to genomic medicine expertise and testing
- High cost and lack of reimbursement for genetic/genomic tests and services
- Accessibility and relevance of genetic/genomic testing and interpretation to under-served and non-European ancestry populations
- Potentially overwhelming and rapidly evolving nature of genomic information
- Need for extensive informatics and infrastructure to support electronic medical record integration of genomic results and clinical decision support
- Limited evidence of the effectiveness of using genomic information in clinical care
- Lack of institutional and clinician acceptance
- Potential burden of following-up genotyped patients as clinical significance of genomic variants changes or becomes clear
- Potential responsibility for outreach to at-risk family members
- Community perceptions and concerns regarding adequate consent, patient privacy and confidentiality, and potential discrimination

Box 2. Clinically important genomic variation https://www.yourgenome.org/facts/what-types-of-mutation-are-there https://ghr.nlm.nih.gov/primer/mutationsanddisorders/possiblemutations

Single-nucleotide variants: One base replaced by another

Synonymous: no change in the encoded amino acid

Missense: change in the encoded amino acid

Nonsense: premature termination of the peptide chain

Splice site: variant occurring at the boundary of an exon and an intron (splice site) which can disrupt RNA splicing resulting in loss of exons or inclusion of introns and an altered protein-coding sequence [76]

Structural variants

Deletion: one or more bases deleted from the sequence

Insertion: one or more bases added to the sequence

Duplication: segment of DNA copied abnormally one or more times

Frameshift: addition or deletion of 1 or 2 bases (or any number not a multiple of 3) that shifts the reading frame of three bases per amino acid, producing an altered or truncated protein

Expansion: short DNA sequences repeated many times

Inversion: a chromosomal segment reversed end-to-end

Table 1.

Spectrum of gene-disease research and implementation

Discovery Research	**Clinical Validation**	**Clinical Implementation**
Assess genotype-phenotype associations	**Assess outcomes after using genomics to direct therapy**	**Develop processes for performing genomic testing and using results in clinical care**
Identify persons at increased risk of disease based on their genomic variants	Assess impact of genomic information on health outcomes and care utilization for patients, families, providers, healthcare systems (clinical utility)	Develop clinical informatics systems for reporting genomic results and decision support
Find all variants related to given phenotype or disease	Identify causes of rare or undiagnosed diseases	Educate clinicians and patients in clinical use of genomic results
Characterize variation and function of genes known to be related to disease or treatment response	Validate drug targets and develop improved therapeutic agents	Define and disseminate information on clinically actionable genomic variants and relevant evidence base

Table 2.

Indications for single-gene, gene panel, exome, and genome sequencing (after [32]).

Sequencing Test	Indications	Examples
Single gene	• Minimal locus heterogeneity—only one or a small number of genes known to cause the condition	*CFTR* for cystic fibrosis
	• Distinctive clinical findings clearly point to specific gene	*PAH* for phenylketonuria
Gene panel	• Locus heterogeneity—multiple genes known to cause same or similar condition	Muscular dystrophy panel
	• Disorders with overlapping phenotypes	Cardiomyopathy panel
	• Disorders sharing one manifestation but often very different presentations	Epilepsy panel
	• Disorders associated with genes from a common pathway or structure	*RAS*opathy panel
Exome	• Extreme heterogeneity and *de novo* mutations are often found	Autism, intellectual disability
	• Two or more unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia
	• No distinctive phenotypic feature present	Kabuki syndrome
	• Phenotype indistinct and underlying cause not clear	Congenital diarrhea, Zellweger syndrome
Genome	As above for exome, plus: • Non-coding variation suspected as a cause	Hypertrophic cardiomyopathy [77]
	• Structural variation suspected as a cause	DiGeorge syndrome [24]
	• Exome sequencing already performed and nondiagnostic	Undiagnosed Diseases Network [33]
	• Rapid generation of sequencing data in critically ill patients	Neonatal intensive care patients [5]

Table 3.

Classifications of pathogenicity of genomic variants [42].

Classification	Meaning
Pathogenic	Greater than 99% certainty of a variant being disease causing
Likely pathogenic	Greater than 90% certainty of a variant being disease causing
Unknown significance	Certainty between 10% and 90% of being disease causing
Likely benign	Greater than 90% certainty of a variant not being disease causing
Benign	Greater than 99% certainty of a variant not being disease causing

Table 4.

Examples of genomic resources by constituency.

	CONSTITUENCY				
Resource Type	**Patients and Family Members**	**Clinicians**	**Geneticists and Genetic Counselors**	**Diagnostic Laboratory Scientists**	**Genomics Researchers**
Clinical reference resources	Genetics Home Reference (GHR) ghr.nlm.nih.gov	MedGen https://www.ncbi.nlm.nih.gov/medgen/ Genetic Testing Registry (GTR) https://www.ncbi.nlm.nih.gov/gtr/ Clinical Pharmacogenetics Implementation Consortium https://cpicpgx.org/	Online Mendelian Inheritance in Man (OMIM) www.ncbi.nlm.nih.gov/omim	ClinGen https://www.clinicalgenome.org/ ClinVar ht/www.ncbi.nlm.nih.gov/clinvar/	GeneCards (http://www.genecards.org) PharmGKB https://www.pharmgkb.org/ The Cancer Genome Atlas (TCGA) https://cancergenome.nih.gov/
Educational resources	NHGRI Talking Glossary https://www.genome.gov/glossary/ Your Genome www.yourgenome.org Genetic Alliance http://www.geneticalliance.org/	Genetics/Genomics Competency Center https://genomicseducation.net/ GeneReviews http://www.genereviews.org			
Data resources	GenomeConnect https://www.genomeconnect.org/ MyGene2 (https://mygene2.org/MyGene2/		Matchmaker Exchange https://www.matchmakerexchange.org/	gnomAD http://gnomad.broadinstitute.org/	Gene-Tissue Expression Project (GTEx) http://www.gtexportal.org/home Alliance of Genome Resources https://www.alliancegenome.org/ Monarch Initiative https://monarchinitiative.org/

Table 5.

NHGRI genomic medicine research programs and associated NIH funding and fiscal year (FY) of support, 2007–2022. Amounts for FY2019 and beyond are estimates.

Program NIH Funding and Fiscal Years (FY) of Support	Objectives	Website URL
Undiagnosed Diseases Network (UDN)[1] $237M, FY2013-FY2022	• Build upon NIH Undiagnosed Diseases Program to improve diagnosis and care for patients with undiagnosed diseases • Facilitate research into the etiology of undiagnosed diseases • Create an integrated and collaborative research community to identify improved options for optimal patient management • Assess development of a sustainable national resource after NIH support ends in FY22	https://undiagnosed.hms.harvard.edu/
Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)[2] $26M, FY2013-FY2018	• Explore implications, opportunities, and challenges of using genomic sequence information in the newborn period • Acquire, analyze, and make available genomic datasets relevant to the newborn period • Advance understanding of disorders identifiable via sequenced-based newborn screening • Investigate ELSI implications of implementation of genomic sequencing of newborns	https://www.genome.gov/27558493/newborn-sequencing-in-genomic-medicine-and-public-health-nsight/
Clinical Sequencing Evidence-Generating Research (CSER)[3] $166M, FY2012-FY2020	• Define, generate and analyze evidence regarding clinical utility of genome sequencing • Research critical interactions among patients, family projects members, health practitioners, and clinical laboratories that influence implementation of clinical genome sequencing • Identify and address real-world barriers to integrating genomic, clinical, and healthcare utilization data within a healthcare system	https://cser-consortium.org/projects
Electronic Medical Records and Genomics Network (eMERGE)[4] $141M, FY2007–2019	• Identify rare variants with presumed major impact on function of 100 clinically relevant genes • Assess phenotypic implications of variants by leveraging well-validated EMR data or re-contact • With appropriate consent and education, report actionable variants to patients and clinicians • Assess impact to patients, clinicians, and institutions on patient outcomes and cost of care	https://emerge.mc.vanderbilt.edu/
Implementing Genomics in Practice (IGNITE) $35M, FY2013-FY2018	• Expand and link existing genomic medicine efforts • Develop new collaborative projects and methods in diverse settings and populations • Contribute to evidence base regarding outcomes of incorporating genomic information into clinical care • Define and share processes of genomic medicine implementation, diffusion, and sustainability	https://ignite-genomics.org/
Implementing Genomics in Practice (IGNITE)-Pragmatic Clinical Trials $41M, FY2018-FY2022	• Conduct pragmatic clinical trials to measure clinical utility and cost-effectiveness of genomic medicine interventions • Assess approaches for real-world application of genomic medicine in diverse clinical settings • Identify types of interventions requiring randomized trials and effective methods for conducting them	https://www.genome.gov/27572183/
Clinical Genome Resource (ClinGen)[5] $73M, FY2013-FY2020	• Create a comprehensive, openly accessible knowledge base of clinically annotated genes and variants • Develop consensus process for assessing clinical implications of genetic variants • Disseminate this information to appropriate clinical organizations to aid in developing practice guidelines • Build upon and unify existing efforts to interpret clinical implications of sequence variants	https://www.clinicalgenome.org/
Investigator-Initiated Research $42M, FY15-FY2022	• Perform clinical sequencing research • Identify genomic determinants of HIV/AIDS drug response and co-morbidities • Examine genomic associations of serious adverse drug reactions and develop preventive strategies	https://www.genome.gov/27530165/
Training and Education $16M, FY2016-FY2021	• Establish institutional training grants • Support fellowships	https://www.genome.gov/10000950/

Program NIH Funding and Fiscal Years (FY) of Support	Objectives	Website URL
	• Conduct conferences	

[1] Supported by the NIH Common Fund

[2] Co-funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development

[3] Co-funded by the National Cancer Institute

[4] Co-funded by the NIH Office of the Director

[5] Co-funded by the National Cancer Institute and the NIH Office of the Director