Genomic Medicine 1

Opportunities, resources, and techniques for implementing genomics in clinical care

Teri A Manolio, Robb Rowley, Marc S Williams, Dan Roden, Geoffrey S Ginsburg, Carol Bult, Rex L Chisholm, Patricia A Deverka, Howard L McLeod, George A Mensah, Mary V Relling, Laura Lyman Rodriguez, Cecelia Tamburro, Eric D Green

Advances in technologies for assessing genomic variation and an increasing understanding of the effects of genomic variants on health and disease are driving the transition of genomics from the research laboratory into clinical care. Genomic medicine, or the use of an individual's genomic information as part of their clinical care, is increasingly gaining acceptance in routine practice, including in assessing disease risk in individuals and their families, diagnosing rare and undiagnosed diseases, and improving drug safety and efficacy. We describe the major types and measurement tools of genomic variation that are currently of clinical importance, review approaches to interpreting genomic sequence variants, identify publicly available tools and resources for genomic test interpretation, and discuss several key barriers in using genomic information in routine clinical practice.

Lancet 2019; 394: 511–20

Published Online August 5, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31140-7

This is the first in a Series of five papers about genomic medicine

National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA (Prof T A Manolio MD, R Rowley MD, L L Rodriguez PhD, C Tamburro BA, E D Green MD); **Genomic Medicine Institute, Geisinger, Danville, PA, USA** (Prof M S Williams MD); **Department of Medicine, Department of Pharmacology, and Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, USA** (Prof D Roden MD); **Duke Center for Applied Genomic and Precision Medicine, Duke University, Durham, NC, USA** (Prof G S Ginsburg MD); **The Jackson Laboratory for Mammalian Genetics, Bar Harbor, ME, USA** (Prof C Bult PhD); **Center for Genetic Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA** (Rex L Chisholm PhD); **American Institutes for Research, Washington, DC, USA** (P A Deverka MD); **DeBartolo Family Personalized Medicine Institute, Moffitt Cancer Center, Tampa, FL, USA** (Prof H L McLeod PharmD); **Center for Translation Research and Implementation Science, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA** (Prof G A Mensah MD); **and Pharmaceutical Sciences Department, St Jude Children's Research Hospital, Memphis, TN, USA** (Prof M V Relling PharmD)

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. A broad range of research and implementation efforts are underway, including discovery research to assess genotype–phenotype associations, clinical validation to assess 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 (panel 1). Clinical validation and implementation in particular are considered by the US National Human Genome Research Institute (NHGRI) to constitute genomic medicine, which is defined by NHGRI as using genomic information about an individual as part of their clinical care.[1] A widening array of genomic medicine applications is gaining acceptance in routine care, including in 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 (panel 2).[1,8–10] Efforts in the USA and other countries are addressing some of these challenges,[11–15] such as the UK's 100 000 Genomes Project[14] that is bringing whole genome sequencing directly into clinical care. As genomic medicine technologies and methods become increasingly accessible, clinicians will need to understand these new tools and adapt them to suit specific practice settings.

This is the first in a Series of five papers designed to introduce practicing clinicians to the opportunities and challenges of genomic medicine implementation. In this first paper, we provide an overview of 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. The four subsequent papers in the Series will focus on improving drug safety and efficacy,[16] diagnosing rare and undiagnosed diseases,[17] assessing disease risk,[18] and assessing outcomes of implementation.[19] The use of tumour genomic sequence variants for targeted chemotherapy and informing eligibility for clinical trials,[20] and genome sequencing for the identification and sensitivity testing of infectious agents,[21] has been in clinical practice for several years and will not be addressed in this Series.

Key technologies in genomic medicine

Family health history

Although 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 recognised since the time of Hippocrates.[22] Family health history is one of the simplest, cheapest, and most predictive types of genomic information to collect, yet it is rarely available in medical records aside from a cursory mention, such as "father died age 61, stroke". It is rarely represented as structured data that can be easily retrieved computationally. However, a family history of early coronary disease or cancer, especially among multiple relatives, often confers an increased risk that is many times greater than that conferred by the majority of known genomic variants.[23,24] Several user-friendly, patient-facing family history tools are available[25,26] and have been shown to be powerful identifiers of increased risk for a variety of serious diseases.[3,24] Although a patient-entered family history does not conform to the high-tech nature of other genomic technologies, it serves as a basic assay of the effect of a patient's genomic variants in the other people who are most likely to carry them—ie, their biological relatives. It also captures the effects of shared

Panel 1: **Types of genomic medicine research**

Discovery research
- Assess genotype–phenotype associations
- Identify people who are at increased risk of disease on the basis of their genomic variants
- Find all variants related to a given phenotype or disease
- Characterise variation and function of genes known to be related to a disease or treatment response

Clinical validation
- Assess outcomes after use of genomics to direct therapy
- Assess effects of genomic information on health outcomes and care utilisation for patients, families, providers, and health-care systems (clinical utility)
- Identify causes of rare or undiagnosed diseases
- Validate drug targets and develop improved therapeutic agents

Clinical implementation
- Develop processes for doing genomic testing and using results in clinical care
- Develop clinical informatics systems for reporting genomic results and decision support
- Educate clinicians and patients in clinical use of genomic results
- Define and disseminate information on clinically actionable genomic variants and relevant evidence base

Panel 2: **Challenges to implementation of genomic medicine**[1]

- Lack of familiarity and understanding by patients and clinicians
- Poor access to genomic medicine expertise and testing
- High cost and lack of reimbursement for genetic or genomic tests and services
- Accessibility and relevance of genetic or genomic testing and interpretation to under-represented and non-European populations
- Potentially overwhelming and rapidly evolving nature of genomic information
- Need for extensive informatics and infrastructure to integrate genomic results into electronic medical records and provide clinical decision support
- Little evidence of the effectiveness of using genomic information in clinical care
- Non-acceptance of genomic medicine by institutions and clinicians
- Potential burden of following up genotyped patients when the clinical significance of genomic variants changes or becomes clear
- Potential responsibility for outreach to at-risk family members
- Community perceptions and concerns regarding consent, patient privacy and confidentiality, and discrimination

Correspondence to:
Prof Teri A Manolio, Division of Genomic Medicine, National Human Genome Research Institute, Bethesda, MD 20892, USA
manolio@nih.gov

environmental exposures, is relatively easy and inexpensive to collect, and has demonstrated reliability.[27] The use of family health histories is discussed further in the fourth paper in this Series.[18]

Clinically important genomic variation

Genomic technologies are used to identify variants in genomic sequences. The types of variants that could be clinically important can be divided two main categories. The first category of variants involves changes to the coding regions of genes (known as exons), which can render a gene's protein product(s) inactive (known as loss of function) or aberrantly active (known as gain of function). A change of one base pair in the sequence is referred to as a single nucleotide polymorphism (SNP), and it can lead to loss-of-function variants, such as missense or nonsense variants that inactivate or impair the function of the gene's protein product (panel 3). For instance, the adenine-to-thymine transversion in the codon for amino acid 6 of the haemoglobin subunit beta gene results in the production of sickle haemoglobin. Although the vast majority of DNA variants are SNPs, variants can also be insertions or deletions of one or two base pairs, resulting in a so-called frameshift that alters the way the sequence is read during transcription and can prematurely terminate the protein product. Alternatively, a single-base change at a splice site can impair correct assembly of the messenger RNA to code that protein. Larger deletions, which can be thousands or even millions of base pairs in length, can also be clinically important if they remove a chromosomal region needed for normal function. For instance, the chromosome 22q11.2 deletion produces distinctive phenotypes, such as DiGeorge and velocardiofacial syndromes.[29] Larger insertions can introduce an extra copy of a gene whose protein product (often an enzyme) can 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.[30]

The second type of genomic variation involves changes in the non-coding sequences that make up 98% of the human genome. Key functional elements in non-coding DNA include promoters, enhancers, transcription factor binding sites, and non-coding RNAs, all of which can influence the amount of gene product made. Although they are not direct changes to the DNA sequence, epigenetic changes to nucleotides or their associated proteins (eg, methylation of cytosine residues or variation in the histone proteins that package DNA into chromosomes) can affect the accessibility of DNA segments for transcription, resulting in reduced or eliminated transcription. The relevance of non-coding variants to clinical care is only beginning to be understood and will not be addressed in detail 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, for which the sequences have been defined through haplotype mapping efforts.[31] Identifying a single SNP in a haplotype region often allows the surrounding sequence to be inferred with high accuracy. These so-called 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 test for the presence of hundreds of thousands, or even millions, of genomic variants. In addition to directly evaluating SNPs, the availability of reference sequence databases has enabled accurate imputation of common sequence variation, or variants that are 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 on the basis of previously estimated relationships with neighbouring measured variants. Imputation is most accurate when the sequences surrounding these known variants are well characterised. Of note, sequence information in populations of non-European ancestry is less complete than in European populations.[32]

First introduced for research use in 2005, genome-wide SNP arrays have been used in thousands of genome-wide association studies. These studies have identified tag SNPs associated with numerous diseases and traits and have led to many critical discoveries about the role of genomic variation in health and disease.[33] Genome-wide SNP arrays are now in clinical use and are largely replacing karyotyping for detection of aneuploidies and large chromosomal aberrations. They have been combined into panels for assessing variants in genes involved in drug response (so-called pharmacogenes, which are the subject of the second paper in this Series[16]) and risk for 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 are the cheapest method for characterising common (and with imputation, 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 populations of non-European ancestry on SNP arrays.[32]

Genome sequencing

Although they have many strengths, SNPs have several weaknesses that might limit their value in individual patients, particularly when the genomic variation underlying a patient's condition is rare. SNP arrays assess only known (ie, previously identified) SNPs, which are typically those that are present in a large proportion of a population, rather than those variants that are rare or even unique to an individual. SNP arrays also rely on accurate reference databases for imputing the surrounding variants that are not directly assayed by the array. Therefore, they are less precise for examining some genomic regions, such as those with 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 is frequently associated with a common tag SNP. As noted previously, arrays are heavily biased towards populations of European ancestry.

Genome sequencing addresses many of the disadvantages of SNP arrays. Theoretically, genome sequencing produces a base-by-base read-out of every nucleotide in the genome. In practice, some chromosomal regions are technically difficult to sequence reliably, particularly highly repetitive regions and areas of high guanine and cytosine content, although technologies continue to improve.[34] Sequencing methods are continuously evolving and a review of them is outside the scope of this paper; however, authoritative reviews are available.[35,36] Understanding sequencing technologies is not critical to understanding their clinical applications, although the person or organisation ordering a genome sequence does need to understand the strengths and weaknesses of a given method to ensure it is appropriate to the setting. This understanding is best ascertained by consulting a molecular pathologist proficient in genomic analysis or through discussion with the laboratory that is going to perform the test.

Four main types of DNA sequencing 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 1).[39] Single gene assays and targeted gene panels are mostly used when one gene or a small group of genes is strongly implicated by a patient's clinical characteristics, whereas exome and genome sequencing are used when clinical characteristics do not clearly indicate one gene or group of genes, or when other methods have failed to identify a causative variant, or both. In comparison with exome sequencing, genome sequencing provides more even coverage across the genome. Therefore, it avoids the problems of differential amplification of difficult-to-sequence genomic segments and preferential capture of reference alleles (rather than alternative alleles) that affect targeted methods.[34,38] Other advantages of genome sequencing over exome sequencing include better resolution of structural variants, such as insertions and deletions, and faster generation of sequence data,[5] although genome sequencing methods produce substantially more data that require interpretation. The biggest disadvantage of genome sequencing is the high cost. Interpretation of both exome and genome sequencing is facilitated by trio analysis, in which sequencing is done for the index patient and both of his or her parents. Trio

Panel 3: **Types of clinically important genomic variation**

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 and result in the loss of exons or inclusion of introns and an altered protein-coding sequence[28]

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 one or two bases (or any number that is not a multiple of three) 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

	Example
Single gene	
Minimal locus heterogeneity (only one or a small number of genes is known to cause the condition)	*CFTR* for cystic fibrosis
Distinctive clinical findings that clearly indicate a specific gene	*PAH* for phenylketonuria
Gene panel	
Locus heterogeneity (multiple genes are known to cause the same condition or similar conditions)	Muscular dystrophy panel
Disorders with overlapping phenotypes	Cardiomyopathy panel
Disorders that share one manifestation but can have very different presentations	Epilepsy panel
Disorders associated with genes from a common pathway or structure	RASopathy panel
Exome	
Extreme heterogeneity and de novo mutations common	Autism, intellectual disability
Two or more unrelated phenotypes in one patient	Oculocutaneous albinism and neutropenia
No distinctive phenotypic features present	Kabuki syndrome
Phenotype indistinct and underlying cause is not clear	Congenital diarrhoea, Zellweger syndrome
Genome*	
Non-coding variation is suspected as a cause	Hypertrophic cardiomyopathy[37]
Structural variation is suspected as a cause	DiGeorge syndrome[29]
Exome sequencing has already been performed and was non-diagnostic	Undiagnosed Diseases Network[38]
Rapid generation of sequencing data needed for patients who are critically ill	Neonates in intensive care[5]

*Indications for exome also apply to genome, with the addition of those listed below.

Table 1: **Indications for single gene, gene panel, exome, and genome sequencing[39]**

	Definition
Pathogenic	>99% certainty of being disease-causing
Likely pathogenic	>90% certainty of being disease-causing
Unknown significance	10–90% certainty of being disease-causing
Likely benign	>90% certainty of not being disease-causing
Benign	>99% certainty of not being disease-causing

Table 2: **Classifications of pathogenicity for genomic variants[48]**

analysis allows rapid identification of de novo variants that arise during gametogenesis and embryogenesis in the child.[40] A complementary high-throughput sequencing method, RNAseq, quantifies RNA transcripts to assess gene expression. It is showing promise in detecting non-coding variants in cancer and neuromuscular diseases,[41–43] but it is not widely available in clinical settings at present.

The choice of sequencing method is often driven by costs and reimbursement policies, although prices quoted for single-gene and gene-panel sequencing can often approach or exceed more comprehensive methods (exome and genome sequencing), for which costs are continually decreasing. In addition, the choice of method could be influenced by the informatics capabilities of the sequencing laboratory, because exome and genome sequence analyses are computationally intensive, with substantial 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, because each genome has 4–5 million variants, tens or hundreds of thousands of which are rare (a population frequency of <0·5%). Sorting through and interpreting variants that have rarely or never been identified before, and for which the clinical relevance is unknown, is a huge informatics challenge. Furthermore, the process requires continuous updating and reinterpretation as the understanding of sequence variants increases. Sharing of data on variants and their phenotypic associations among clinicians and researchers is crucial to improving interpretation of variants, because the more times a variant is reported and the better defined its associated phenotypes are, the more reliable the classification will be. In particular, data from ancestrally diverse populations needs to be shared, because if a variant is rare in one ancestry but common in another, it is unlikely to cause an uncommon disease.[44] Laboratories, clinicians, and patients are strongly encouraged to deposit sequencing information into large-scale, de-identified, publicly available data resources (such as those described later) to improve the quality of genome interpretation.

Interpretation of genomic variants

Assessing pathogenicity of variants

As noted previously, sequencing part or all of an individual's genome can produce several million variants in comparison with the reference sequence; thousands of these variants will have little or no available information in current databases.[45,46] Determining which of these variants could cause a particular phenotype, or could put the person at risk for a serious illness or an adverse drug response, is a complicated process. First, the quality and validity of the generated sequence data and the identified variants must be carefully checked.[47] Typically, the next step is to filter out variants that are unlikely to cause disease, usually because they occur at a frequency much higher than the population frequency of the disease or phenotype under consideration.[47] Further interpretation usually 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,[48] which divides variants into those that are clearly disease-causing (pathogenic), clearly non-disease-causing (benign), or for which the relationship to disease is unknown (variants of unknown significance [VUS]). If the pathogenicity of a variant is not known but can be inferred because it is believed to have the same effect on gene function as a variant that has previously been classified, it is classified as likely pathogenic (LP) or likely benign (LB; table 2).

This five-tiered classification scheme has been derived with use of data from a wide variety of sources (eg, population data, functional data, in silico functional predictors, and segregation data) that have been combined using a series of scoring rules to assign points in a complex but systematic way.[48] Of note, the ACMG guidelines are not intended for the interpretation of

variants that are found only in specific tissues or in tumours (often called somatic variants, as opposed to germline or inherited variants that are found in every cell of the body). The ACMG guidelines also do not apply to pharmacogenomic variants, which are interpreted with use of clinical prescribing guidelines by the Clinical Pharmacogenetics Implementation Consortium.[49]

The large class of VUS is problematic because their clinical relevance is truly unknown, even when they occur in a known disease-causing gene, such as *BRCA1* (causing hereditary breast and ovarian cancer) or *COL3A1* (causing vascular Ehlers-Danlos syndrome). Because each individual carries millions of variants, many variants will occur within such disease-causing genes by chance, especially if those genes are large. When variants are detected in a patient with a phenotype that is presumably related to that disease-causing gene, VUS can sometimes be misinterpreted as causing the phenotype when in fact they are totally coincidential and unrelated. This can then lead clinicians to believe that drastic interventions such as mastectomy or implantable defibrillators are indicated when there is no evidence to support their efficacy. However, an awareness of such variants can be important if information becomes available later that shifts them into the pathogenic or LP classification, a situation that is arising more often as knowledge about genomic variation increases.[50,51] Shifts can also occur between more definitive classifications, such as benign or LB to pathogenic or LP and vice versa, which can have important implications for clinical management. Such changes have been infrequent to date,[50] but they could become more common as data accumulate. A consensus is yet to be found on the appropriate frequency and intensity with which data should be reinterpreted, or which types of evidence are the most informative. Nevertheless, reclassification on the basis of new biological knowledge or changing clinical circumstances is crucial, and presents a challenge to clinicians and patients who are trying to act on the basis of genomic variant information.[51,52]

Most US laboratories now report gene variants that are classified as pathogenic or LP, and which occur in a gene likely to be responsible for a patient's clinical characteristics, as primary findings (ie, findings related to the indication for testing). However, because researchers are often looking at large segments of the genome, they also identify pathogenic or LP variants in other genes that are unrelated to the indication for sequencing (secondary findings), but which could be strongly predictive of risk for other diseases. ACMG has identified 59 such genes, for which pathogenic or 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 the frequency of surveillance are recognised to be beneficial.[53] Many laboratories feel compelled to report these secondary findings as recommended by ACMG guidelines, yet they recognise that not all such variants cause disease in every patient, a characteristic referred to as variable penetrance. ACMG and other expert bodies specifically recommend against returning VUS (as opposed to pathogenic and LP variants) as secondary findings, because of the problems with misinterpretation detailed previously.[53]

Practical uses of variant information

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 effective clinical action can be taken. However, the definition of effective clinical action is subjective, and relies on both context and clinical judgment. For example, a reasonable clinical action could differ considerably for a person who is trying to conceive, an elderly person with a terminal disease, and a healthy young child. Actionability and reporting of genomic variation are topics of intense interest and debate in children in particular;[54,55] several secondary findings could be relevant to the management of children, including genes related to familial hypercholesterolaemia, cardiomyopathy, early onset cancers, and cardiac arrhythmias. Personal choices vary considerably, with some individuals wanting to receive all variant information available, with any possible personal implications (eg, in informing lifestyle choices), and others preferring not to receive any information at all.[56] Standards for actionability have been published by the NHGRI-funded Clinical Genome Resource (ClinGen),[57] which assigns variants a grade on the basis of its characteristics (ie, the severity of the condition associated with the variant, the likelihood that disease will develop in variant carriers, the effectiveness of available interventions, and the nature [or invasiveness] of the available interventions), and the strength of available evidence for these characteristics. Although personal choices will still vary, this grading provides a framework for discussing what results patients are willing to receive and how those wishes might change over a patient's lifetime.

For the **Clinical Pharmacogenetics Implementation Consortium** see https://cpicpgx.org

For **ClinGen** see https://www.clinicalgenome.org

Return of genomic research results

The process of returning genomic results to patients and clinicians (especially those derived from research studies) has been the subject of almost as much research as the actionability of the variants. Considerable debate continues on what information should be returned, to whom and by whom it should be returned, and how and when this should happen.[58,59] These issues can be particularly difficult to resolve when children or infants are involved.[60,61] Ethical concerns, such as the duty to warn first-degree relatives of people carrying pathogenic or LP variants for serious and preventable illnesses (who will have approximately a 50% chance of also carrying those variants), must be balanced against the right of a patient or research participant to privacy and confidentiality. Increasingly, the consensus among researchers, clinicians, and patients is that patients have the right to receive genomic information with clear implications for

their health, and the right to refuse that information; such results should be derived from clinically validated and certified processes; and counselling on the potential implications of these findings should be provided both before patients agree to undergo testing and after they receive the results.[62,63] Once a pathogenic or LP variant is identified in an individual, family members can be screened for it; if family members are considering being tested, they should also receive genetic counselling. Many concerns have been raised about the potential harmful effects of receiving genetic results,[63] which often stem from early negative experiences with severe and irreversible monogenic conditions. However, communicating genetic risk for disease has largely not been shown to affect risk-reducing behaviours or to result in depression or anxiety.[64,65] Research in the potential health benefits is currently ongoing. The return of genomic results will remain an active area of research as the quantity and quality of genomic information continues to evolve.

For **GeneReviews** see http://www.genereviews.org

Genomic resources

Many different groups of people are affected by advances in genomic technologies, from patients and their families to clinicians, geneticists, laboratory scientists, and genomics researchers. A broad range of resources are available to these groups for clinical reference, education, and data sharing (table 3, appendix). The number and usefulness of such resources are steadily increasing.

See Online for appendix

For the **Matchmaker Exchange** see https://www.matchmakerexchange.org

For the **Genetics Home Reference** see https://ghr.nlm.nih.gov

For the **Genome Aggregation Database** see http://gnomad.broadinstitute.org

For **MedGen** see https://www.ncbi.nlm.nih.gov/medgen

For the **Genetic Testing Registry** see https://www.ncbi.nlm.nih.gov/gtr

For the **Online Mendelian Inheritance in Man database** see www.ncbi.nlm.nih.gov/omim

For **ClinVar** see https://www.ncbi.nlm.nih.gov/clinvar

For the **MyCode Community Health Initiative** see https://www.geisinger.org/mycode

For the **100 000 Genomes Project** see https://www.genomicsengland.co.uk

For **GeneCards** see http://www.genecards.org

For **PharmGKB** see https://www.pharmgkb.org

For **The Cancer Genome Atlas** see https://cancergenome.nih.gov

First-line clinical information is crucial for recently diagnosed patients and their families. For example, the Genetics Home Reference of the US National Library of Medicine (NLM) provides basic information on health conditions with a genetic basis. For clinicians who are not genetics specialists, the medical effects of genomic variants can be found in NLM's MedGen. Clinicians can search for available genomic or genetic tests and testing laboratories in the NLM Genetic Testing Registry. Pharmacogenomic information on variants related to drug selection and dosing is available through the Clinical Pharmacogenetics Implementation Consortium website. Advanced clinicians and genetics specialists, including genetic counsellors, are likely to search the Online Mendelian Inheritance in Man database for detailed information on gene–disease relationships, whereas laboratories and clinicians might refer to NLM's ClinVar, which is a public archive of reported variants, associated clinical characteristics, and pathogenicity interpretations. Consensus interpretations of the clinical actionability of variants build upon information in ClinVar and are 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. More specialised resources are available for the subset of genes related to drug response (eg, PharmGKB) and cancer (eg, The Cancer Genome Atlas). The BRCA Exchange resource for interpretation of *BRCA* variants[66] provides a novel approach to aggregating data for real-time variant classification. A simplified interface is also available through a mobile app, which can be used to search the database and request notifications of updates on specific variants. A summary of all genomic databases is beyond the scope of this paper; however, a comprehensive list with descriptions and links is available from the Human Genome Variation Society.[67]

Educational resources are important for patients and non-geneticist clinicians. Available resources include the NHGRI Talking Glossary of Genetic Terms, Your Genome, Genetic Alliance, the Genetics/Genomics Competency Center, and GeneReviews. Data sharing has also been essential for determining the functionality of variants and identifying the clinical characteristics associated with disease-causing variants. Several data-sharing resources are available, including GenomeConnect and MyGene2. These sites allow patients to deposit their own genomic data and clinical characteristics in an open, public database in the hope that their information is useful to other patients, clinicians, and researchers. Clinicians (typically geneticists) who encounter an undiagnosed patient with a novel genomic variant often need only one additional case with a pathogenic or LP variant in the same gene and similar clinical characteristics to identify the causative gene; they can seek such patients with use of tools such as the Matchmaker Exchange. These tools can be especially useful for managing genomic information in patients with undiagnosed diseases, which is the subject of the third paper in this Series.[17]

Laboratories contribute data to growing community resources, such as NLM's ClinVar. They can also use compiled resources, such as the Genome Aggregation Database, to determine whether a variant has previously been detected and, if so, at what frequency across ancestries. According to ACMG guidelines, variants will be classified as benign if they are too common in a population to cause a rare disease.[48] Researchers can also consult specific data resources, such as the Gene-Tissue Expression database that describes gene expression and its genetic regulation in more than 50 human tissue types, or the Monarch Initiative and the Alliance of Genome Resources 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 USA and elsewhere, as reviewed by Stark and colleagues.[68] The Geisinger MyCode Community Health Initiative and the Genomics England 100 000 Genomes Project have each sequenced over 100 000 genomes and the results are being used in clinical care. In 2018, the Genomics England project was expanded to 5 000 000 genomes. Similar projects in other medical systems and other countries are likely to be initiated soon.

Building on its 2011 strategic plan,[69] NHGRI has expanded existing research programmes into genomic

	Patients and family members	Clinicians	Geneticists and genetic counsellors	Diagnostic laboratory scientists	Genomics researchers
Clinical reference resources	Genetics Home Reference	MedGen, Genetic Testing Registry, Clinical Pharmacogenetics Implementation Consortium	Online Mendelian Inheritance in Man	Clinical Genome Resource, ClinVar	GeneCards, PharmGKB, The Cancer Genome Atlas
Educational resources	NHGRI Talking Glossary of Genetic Terms, Your Genome, Genetic Alliance	Genetics/Genomics Competency Center, GeneReviews	NA	NA	NA
Data resources	GenomeConnect, MyGene2	NA	Matchmaker Exchange	Genome Aggregation Database	Gene-Tissue Expression Project, Monarch Initiative, Alliance of Genome Resources

NHGRI=National Human Genome Research Institute. NA=not applicable.

Table 3: **Examples of resources for reference, education, and data sharing by user group**

	NIH funding (fiscal years)	Objectives
Undiagnosed Diseases Network[1]	$237 million (2013–22)	Build on the NIH Undiagnosed Diseases Program to improve diagnosis and care for patients with undiagnosed diseases; facilitate research into the causes of undiagnosed diseases; create an integrated and collaborative research community to identify improved options for optimal patient management; assess the development of a sustainable national resource after NIH support ends in fiscal year 2022
Newborn Sequencing in Genomic Medicine and Public Health[2]	$26 million (2013–18)	Explore implications, opportunities, and challenges of using genomic sequence information in the newborn period; acquire, analyse, and make available genomic datasets relevant to the newborn period; advance understanding of disorders identifiable via sequence-based newborn screening; investigate the ethical, legal, and social implications of implementation of genomic sequencing of newborn babies
Clinical Sequencing Evidence-Generating Research[3]	$166 million (2012–20)	Define, generate, and analyse evidence on the clinical utility of genome sequencing; research key interactions among patients, family members, health practitioners, and clinical laboratories that affect the implementation of clinical genome sequencing; identify and address real-world barriers to integrating genomic, clinical, and health-care utilisation data within a health-care system
Electronic Medical Records and Genomics Network[4]	$141 million (2007–19)	Identify rare variants with a presumed major effect on the function of 100 clinically relevant genes; assess the phenotypic implications of variants by use of well validated electronic medical record data or patient recontact; with appropriate consent and education, report actionable variants to patients and clinicians; assess the impact on patients, clinicians, and institutions of patient outcomes and cost of care
IGNITE	$35 million (2013–18)	Expand and link existing genomic medicine efforts; develop new collaborative projects and methods in diverse settings and populations; contribute to the evidence base for outcomes of incorporating genomic information into clinical care; define and share processes of genomic medicine implementation, dissemination, and sustainability
IGNITE Pragmatic Clinical Trials	$41 million (2018–22)	Do pragmatic clinical trials to measure the clinical utility and cost-effectiveness of genomic medicine interventions; assess approaches for the real-world application of genomic medicine in diverse clinical settings; identify types of interventions requiring randomised trials and effective methods for conducting them
Clinical Genome Resource[5]	$73 million (2013–20)	Create a comprehensive, openly accessible knowledge base of clinically annotated genes and variants; develop a consensus process for assessing clinical implications of genetic variants; disseminate this information to appropriate clinical organisations to aid in developing practice guidelines; build on and unify existing efforts to interpret clinical implications of sequence variants
Investigator-initiated research	$42 million (2015–22)	Perform clinical sequencing research; identify genomic determinants of HIV/AIDS drug response and comorbidities; examine genomic associations of serious adverse drug reactions and develop preventive strategies
Training and education	$16 million (2016–21)	Establish institutional training grants; support fellowships; organise conferences

Funding amounts are in US$. Amounts for fiscal year 2019 and later are estimates. NIH=US National Institutes of Health. IGNITE=Implementing Genomics in Practice.

Table 4: **US National Human Genome Research Institute genomic medicine research programmes and associated NIH funding**

medicine implementation and developed others to address key gaps in the research (table 4). These programmes range from those that are highly focused on in-depth characterisation of and interaction with individual patients and their clinicians, such as the Undiagnosed Diseases Network and the Newborn Sequencing in Genomic Medicine and Public Health Consortium, to those that address 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. These research programmes are underpinned by resources and systems for knowledge synthesis and integration, such as ClinGen, as well as by investigator-initiated grants and training programmes. Total funding for genomic medicine research programmes from NHGRI and collaborating US National Institutes of Health departments is expected be at least US$775 million from 2007 to 2022, inclusive.

A major emphasis of NHGRI studies is to develop tools and best practices for genomic medicine implementation and to make them widely available for the research and clinical communities. The Clinical Sequencing Evidence-Generating Research Consortium provides a broad range of online patient education materials and protocol resources. The eMERGE investigators have developed useful tools, such as the Phenotype Knowledge Base of validated electronic phenotyping algorithms and the Clinical Decision Support Knowledge Base of practical, implemented clinical decision support rules. The SPARK Toolbox of the IGNITE Network provides resources for specific interventions (such as *APOL1* testing[70] 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 value and best practices for their use; outcome assessment is explored in detail in the fifth paper in this Series.[19]

Other considerations

Like in many other areas of clinical care, several medical fields and a large number of allied personnel must work together for genomic medicine to be implemented effectively. Informaticians are critical to the integration of genomic information into the electronic health record, as well as to the implementation of effective electronic phenotyping algorithms and clinical decision support.[71] Pharmacists are essential to the effective application of all medical therapeutics, and they are particularly valuable in interpreting pharmacogenetic variants and their impact on drug response.[72] Genetic counselling is a discipline that has evolved in the past 50 years to specifically address the needs of patients who are affected by genomic medicine. The role of the genetic counsellor is to interpret genetic test results, to guide and support patients who are seeking information about how inherited conditions could affect them, and to explain the risks and benefits of specific genetic tests.[73,74] Previously, genetic counsellors worked almost exclusively in partnership with medical geneticists, but as the use of genomic information has extended to common, complex diseases, the need for genetic counsellors and for more streamlined models of providing information to patients has grown considerably. Genetic counsellors are also playing an increasing role in variant interpretation and working with laboratories and health insurers to optimise utilisation of genetic tests.[75]

Multidisciplinary approaches are essential to address some of the key challenges in the use of genomic information in clinical care, such as maintaining confidentiality and minimising the potential for genetic discrimination.[76] Informed consent and adequate genetic counselling on the potential benefits and risks is crucial for all genetic testing and return of results. The risks include discovering an unmodifiable risk of severe disability or early mortality, unsuspected familial relationships, considerable risks to potential offspring that could affect reproductive decision making, or finding no genetic explanation for a patient's condition. The rapid evolution in understanding genomic variation and the dynamic nature of variant interpretation will continue to provide 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 a pathogenic or LP variant in an actionable gene. Primary care physicians are often responsible for the management of these patients, which can be complex and require considerable amounts of time. 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 finding genomic variants in one patient could have profound implications for their family members, effective approaches are needed to communicate such findings to families and facilitate testing of at-risk relatives (known as cascade testing).[77] Health insurers will need to understand and pay for these time-intensive 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 by the US Centers for Disease Control and Prevention for certain modifiable risks (hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolaemia[78]) but has yet to be widely adopted. Testing for these conditions remains focused on patients at risk, who are usually identified through strong family histories, but indications might broaden as knowledge in this field increases.[79] Other challenges in genomic medicine implementation include navigating hurdles to reimbursement from health insurers, 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, data sharing and infrastructure support, improving the regulatory environment, and engaging patients and the public.[80]

Conclusions

Genomic technologies and understanding of genomic variants are continuing to move from the research setting to clinical care in incremental steps that should be viewed as more of an evolution than a revolution. As potential clinical applications of genomic research arise, implementation research is needed to identify 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.[81] Dissemination research is also needed to understand how best to share and sustain knowledge and promote the use of effective interventions. NHGRI collaborates with the National Institutes of Health Dissemination and Implementation Program to fund innovative research in relation to genomic medicine. As medical systems and health-care systems increasingly adopt genomic medicine approaches, data from clinical experiences will become available and could be used to assess the real-world benefits and shortcomings of these approaches.

Numerous resources and materials are available to assist clinicians and patients in adopting genomic medicine approaches. However, accessing and filtering through the large volume of information can be overwhelming. At present, the best option for clinicians might be to contact a local geneticist or genetic counsellor, or a nearby genomics laboratory or molecular pathologist. In the USA, for

instance, these professionals could be located through the ACMG, the US National Society of Genetic Counselors, the College of American Pathology, or the Association for Molecular Pathology. Telemedicine approaches might also meet the growing needs of genomic medicine.[82] Patients are increasingly able to access resources online, and patient support and advocacy groups such as the Genetic Alliance have been effective in directing patients towards appropriate clinical care. Additional training and certification could be offered by medical institutions 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, the adoption and usefulness of genomic information will continue to grow. Concomitantly, clinicians will need to increase their understanding of genomic medicine, which is the intention of this Series.

Contributors

TAM wrote the initial draft. All authors contributed to manuscript organisation, scope, editing of the initial draft, and revisions.

Declaration of interests

MSW reports grants from National Human Genome Research Institute and the National Institutes of Health during the conduct of the study. GSG has stock options in the following companies: Fabric Genomics, Origin Commercial Advisors, Predigen, Exploragen, and Dr Footprint. He receives science advisory board fees from Pappas Ventures and Konica Minolta. HLM reports other fees from Cancer Genetics and Pharmazam, during the conduct of the study, and other fees from Interpares Biomedicine, outside the submitted work. All other authors declare no competing interests.

References

1 Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. *Genet Med* 2013; **15:** 258–67.

2 Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018; **50:** 1219–24.

3 Orlando LA, Wu RR, Myers RA, et al. Clinical utility of a Web-enabled risk-assessment and clinical decision support program. *Genet Med* 2016; **18:** 1020–28.

4 Ramoni RB, Mulvihill JJ, Adams DR, et al. The Undiagnosed Diseases Network: accelerating discovery about health and disease. *Am J Hum Genet* 2017; **100:** 185–92.

5 Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genom Med* 2018; **3:** 6.

6 Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2018; **11:** 181–91.

7 Volpi S, Bult CJ, Chisholm RL, et al. Research directions in the clinical implementation of pharmacogenomics: an overview of US programs and projects. *Clin Pharmacol Ther* 2018; **103:** 778–86.

8 Manolio TA, Abramowicz M, Al-Mulla F, et al. Global implementation of genomic medicine: we are not alone. *Sci Transl Med* 2015; **7:** 290ps13.

9 Ginsburg GS, Phillips KA. Precision medicine: from science to value. *Health Aff (Millwood)* 2018; **37:** 694–701.

10 Owusu Obeng A, Fei K, Levy KD, et al. Physician-reported benefits and barriers to clinical implementation of genomic medicine: a multi-site IGNITE-network survey. *J Pers Med* 2018; **8:** E24.

11 Williams MS, Buchanan AH, Davis FD, et al. Patient-centered precision health in a learning health care system: Geisinger's genomic medicine experience. *Health Aff (Millwood)* 2018; **37:** 757–64.

12 Petrikin JE, Willig LK, Smith LD, Kingsmore SF. Rapid whole genome sequencing and precision neonatology. *Semin Perinatol* 2015; **39:** 623–31.

13 Gaff CL, Winship IM, Forrest SM, et al. Preparing for genomic medicine: a real world demonstration of health system change. *NPJ Genom Med* 2017; **2:** 16.

14 Turnbull C, Scott RH, Thomas E, et al. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ* 2018; **361:** k1687.

15 Manolio TA. Implementing genomics and pharmacogenomics in the clinic: the National Human Genome Research Institute's genomic medicine portfolio. *Atherosclerosis* 2016; **253:** 225–36.

16 Roden DM, McLeod HL, Relling MV, et al. Pharmacogenomics. *Lancet* 2019; published online Aug 5. http://dx.doi.org/10.1016/S0140-6736(19)31276-0.

17 Wise AL, Manolio TA, Mensah GA, et al. Genomic medicine for undiagnosed diseases. *Lancet* 2019; published online Aug 5. http://dx.doi.org/10.1016/S0140-6736(19)31274-7.

18 Ginsburg GS, Wu RR, Orlando LA. Family health history: underused for actionable risk assessment. *Lancet* 2019; published online Aug 5. http://dx.doi.org/10.1016/S0140-6736(19)31275-9.

19 Peterson JF, Roden DM, Orlando LA, Ramirez AH, Mensah GA, Williams MS. Building evidence and measuring clinical outcomes for genomic medicine. *Lancet* 2019; published online Aug 5. http://dx.doi.org/10.1016/S0140-6736(19)31278-4.

20 Damodaran S, Berger MF, Roychowdhury S. Clinical tumor sequencing: opportunities and challenges for precision cancer medicine. *Am Soc Clin Oncol Educ Book* 2015; e175–82.

21 Bentley SD, Parkhill J. Genomic perspectives on the evolution and spread of bacterial pathogens. *Proc Biol Sci* 2015; **282:** 20150488.

22 Pyeritz RE. The family history: the first genetic test, and still useful after all those years? *Genet Med* 2011; **14:** 3–9.

23 Valdez R, Yoon PW, Qureshi N, Green RF, Khoury MJ. Family history in public health practice: a genomic tool for disease prevention and health promotion. *Annu Rev Public Health* 2010; **31:** 69–87.

24 Qureshi N, Armstrong S, Dhiman P, et al. Effect of adding systematic family history enquiry to cardiovascular disease risk assessment in primary care: a matched-pair, cluster randomized trial. *Ann Intern Med* 2012; **156:** 253–62.

25 Welch BM, Wiley K, Pflieger L, et al. Review and comparison of electronic patient-facing family health history tools. *J Genet Couns* 2018; **27:** 381–91.

26 Orlando LA, Buchanan AH, Hahn SE, et al. Development and validation of a primary care-based family health history and decision support program (MeTree). *N C Med J* 2013; **74:** 287–96.

27 Wu RR, Orlando LA. Implementation of health risk assessments with family health history: barriers and benefits. *Postgrad Med J* 2015; **91:** 508–13.

28 National Cancer Institute. NCI Dictionary of Genetics Terms: splice-site variant. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/splice-site-variant (accessed Oct 25, 2018).

29 McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers* 2015; **1:** 15071.

30 Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther* 2014; **95:** 376–82.

31 International HapMap Consortium. The International HapMap Project. *Nature* 2003; **426:** 789–96.

32 Hindorff LA, Bonham VL, Brody LC, et al. Prioritizing diversity in human genomics research. *Nat Rev Genet* 2018; **19:** 175–85.

33 MacArthur J, Bowler E, Cerezo M, et al. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* 2017; **45:** D896–901.

34 Meynert AM, Ansari M, FitzPatrick DR, Taylor MS. Variant detection sensitivity and biases in whole genome and exome sequencing. *BMC Bioinformatics* 2014; **15:** 247.

35 Reuter JA, Spacek DV, Snyder MP. High-throughput sequencing technologies. *Mol Cell* 2015; **58:** 586–97.

36 van Dijk EL, Jaszczyszyn Y, Naquin D, Thermes C. The third revolution in sequencing technology. *Trends Genet* 2018; **34:** 666–81.

37 Mendes de Almeida R, Tavares J, Martins S, et al. Whole gene sequencing identifies deep-intronic variants with potential functional impact in patients with hypertrophic cardiomyopathy. *PLoS One* 2017; **12:** e0182946.

38 Pena LDM, Jiang YH, Schoch K, et al. Looking beyond the exome: a phenotype-first approach to molecular diagnostic resolution in rare and undiagnosed diseases. *Genet Med* 2018; **20:** 464–69.

39 Xue Y, Ankala A, Wilcox WR, Hegde MR. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. *Genet Med* 2015; **17:** 444–51.

40 Acuna-Hidalgo R, Veltman JA, Hoischen A. New insights into the generation and role of de novo mutations in health and disease. *Genome Biol* 2016; **17:** 241.

41 Nakagawa H, Fujita M. Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Sci* 2018; **109:** 513–22.

42 Gonorazky H, Liang M, Cummings B, et al. RNAseq analysis for the diagnosis of muscular dystrophy. *Ann Clin Transl Neurol* 2015; **3:** 55–60.

43 Cummings BB, Marshall JL, Tukiainen T, et al. Improving genetic diagnosis in Mendelian disease with transcriptome sequencing. *Sci Transl Med* 2017; **9:** eaal5209.

44 Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med* 2016; **375:** 655–65.

45 Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016; **536:** 285–91.

46 1000 Genomes Project Consortium, Auton A, Brooks LD, et al. A global reference for human genetic variation. *Nature* 2015; **526:** 68–74.

47 Rehm HL, Bale SJ, Bayrak-Toydemir P, et al. ACMG clinical laboratory standards for next-generation sequencing. *Genet Med* 2013; **15:** 733–47.

48 Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17:** 405–24.

49 Caudle KE, Dunnenberger HM, Freimuth RR, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med* 2017; **19:** 215–23.

50 Aronson SJ, Clark EH, Varugheese M, Baxter S, Babb LJ, Rehm HL. Communicating new knowledge on previously reported genetic variants. *Genet Med* 2012; **14:** 713–19.

51 Chisholm C, Daoud H, Ghani M, et al. Reinterpretation of sequence variants: one diagnostic laboratory's experience, and the need for standard guidelines. *Genet Med* 2018; **20:** 365–68.

52 Matthijs G, Souche E, Alders M, et al. Guidelines for diagnostic next-generation sequencing. *Eur J Hum Genet* 2016; **24:** 2–5.

53 Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med* 2017; **19:** 249–55.

54 Ceyhan-Birsoy O, Murry JB, Machini K, et al. Interpretation of genomic sequencing results in healthy and ill newborns: results from the BabySeq Project. *Am J Hum Genet* 2019; **104:** 76–93.

55 Holm IA, McGuire A, Pereira S, et al. Returning a genomic result for an adult-onset condition to the parents of a newborn: insights from the BabySeq Project. *Pediatrics* 2019; **143** (suppl 1)**:** S37–43.

56 Ramos EM, Din-Lovinescu C, Berg JS, et al. Characterizing genetic variants for clinical action. *Am J Med Genet C Semin Med Genet* 2014; **166C:** 93–104.

57 Hunter JE, Irving SA, Biesecker LG, et al. A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation. *Genet Med* 2016; **18:** 1258–68.

58 Fullerton SM, Wolf WA, Brothers KB, et al. Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network. *Genet Med* 2012; **14:** 424–31.

59 Yu JH, Harrell TM, Jamal SM, Tabor HK, Bamshad MJ. Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. *Am J Hum Genet* 2014; **95:** 77–84.

60 Sénécal K, Rahimzadeh V, Knoppers BM, Fernandez CV, Avard D, Sinnett D. Statement of principles on the return of research results and incidental findings in paediatric research: a multi-site consultative process. *Genome* 2015; **58:** 541–48.

61 Lynch J, Hines J, Theodore S, Mitchell M. Lay attitudes toward trust, uncertainty, and the return of pediatric research results in biobanking. *AJOB Empir Bioeth* 2016; **7:** 160–66.

62 Knoppers BM, Zawati MH, Sénécal K. Return of genetic testing results in the era of whole-genome sequencing. *Nat Rev Genet* 2015; **16:** 553–59.

63 National Academies of Sciences, Engineering, and Medicine. Returning individual research results to participants: guidance for a new research paradigm. Washington, DC: The National Academies Press, 2018.

64 Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ* 2016; **352:** i1102.

65 Marteau TM, French DP, Griffin SJ, et al. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *Cochrane Database Syst Rev* 2010; **10:** CD007275.

66 Cline MS, Liao RG, Parsons MT, et al. BRCA Challenge: BRCA Exchange as a global resource for variants in BRCA1 and BRCA2. *PLoS Genet* 2018; **14:** e1007752.

67 Human Genome Variation Society. Databases and tools. 2019. http://www.hgvs.org/content/databases-tools (accessed June 25, 2019).

68 Stark Z, Dolman L, Manolio TA, et al. Integrating genomics into healthcare: a global responsibility. *Am J Hum Genet* 2019; **104:** 13–20.

69 Green ED, Guyer MS, National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. *Nature* 2011; **470:** 204–13.

70 Horowitz CR, Abul-Husn NS, Ellis S, et al. Determining the effects and challenges of incorporating genetic testing into primary care management of hypertensive patients with African ancestry. *Contemp Clin Trials* 2016; **47:** 101–08.

71 Rasmussen LV, Overby CL, Connolly J, et al. Practical considerations for implementing genomic information resources. Experiences from eMERGE and CSER. *Appl Clin Inform* 2016; **7:** 870–82.

72 Owusu-Obeng A, Weitzel KW, Hatton RC, et al. Emerging roles for pharmacists in clinical implementation of pharmacogenomics. *Pharmacotherapy* 2014; **34:** 1102–12.

73 National Society of Genetic Counselors. Who are genetic counselors? 2018. https://www.nsgc.org/page/whoaregeneticcounselors-473 (accessed June 25, 2019).

74 Mester JL, Schreiber AH, Moran RT. Genetic counselors: your partners in clinical practice. *Cleve Clin J Med* 2012; **79:** 560–68.

75 Reuter C, Grove ME, Orland K, Spoonamore K, Caleshu C. Clinical cardiovascular genetic counselors take a leading role in team-based variant classification. *J Genet Couns* 2018; **27:** 751–60.

76 Wauters A, Van Hoyweghen I. Global trends on fears and concerns of genetic discrimination: a systematic literature review. *J Hum Genet* 2016; **61:** 275–82.

77 Roberts MC, Dotson WD, DeVore CS, et al. Delivery of cascade screening for hereditary conditions: a scoping review of the literature. *Health Aff (Millwood)* 2018; **37:** 801–88.

78 Khoury MJ, Feero WG, Chambers DA, et al. A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health. *PLoS Med* 2018; **15:** e1002631.

79 Abul-Husn NS, Manickam K, Jones LK, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science* 2016; **354:** aaf7000.

80 Dzau VJ, Ginsburg GS, Chopra A, et al. Realizing the full potential of precision medicine in health and health care: a vital direction for health and health care. Washington, DC: National Academy of Medicine, 2016.

81 Roberts MC, Kennedy AE, Chambers DA, Khoury MJ. The current state of implementation science in genomic medicine: opportunities for improvement. *Genet Med* 2017; **19:** 858–63.

82 Vrečar I, Hristovski D, Peterlin B. Telegenetics: an update on availability and use of telemedicine in clinical genetics service. *J Med Syst* 2017; **41:** 21.