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Building evidence and measuring clinical outcomes for genomic medicine

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

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Human genomic sequencing has potential diagnostic, prognostic, and therapeutic value across a wide breadth of clinical disciplines. One barrier to widespread adoption is the paucity of evidence for improved outcomes in patients who do not already have an indication for more focused testing. In this Series paper, we review clinical outcome studies in genomic medicine and discuss the important features and key challenges to building evidence for next generation sequencing in the context of routine patient care.

Introduction

A vision for human genomic medicine is the use of broad-based genetic testing by patients and their health-care providers to enhance routine clinical activities including diagnosis, risk assessment, tailored therapy, and more precise prognosis.[1,2] Rapid advances in laboratory technologies, particularly next generation sequencing, have introduced inexpensive methods to acquire a large set of genetic data with potential applications across many specialties of medicine.[3] Widespread marketing of genomic medicine services and health system implementations have increased the availability of testing to patients and their clinicians.[4–6] However, assessment of the clinical usefulness of genetic testing has not kept pace, leading to questions about the value of returning findings not related to the original indication, and concerns about unintended consequences.[7,8] Paucity of clinical outcome data has been cited as a contributing factor to the slow uptake of genetic testing into clinical guidelines, and inconsistent payer reimbursement policies.[9–12] As some clinicians await further study of verification of benefits, and others adopt testing more readily, the assessment of outcomes is crucial to the future practice of genomic medicine.

Outcome studies should be planned as part of a pipeline from discovery to implementation. Similar to phased drug studies, outcome studies can prospectively validate a discovery, show the efficacy of genome-informed strategies, or assess the effectiveness of an implementation. However, clinical studies of genomic medicine face unique challenges. Firstly, many variants discovered with next generation sequencing are rare (present in less than 1% of the population) and have uncertain association with clinically important health states. Secondly, although germline genetic risks are static and detectable from birth, these risks might be latent and expressed decades after measurement. Large study populations with long duration of follow-up will be needed to address these challenges and capture all relevant health effects. In this Series paper, we describe the methods and challenges to clinical outcome studies related to a genomic medicine practice or intervention. Pharmacogenomics[13] and genetic studies of undiagnosed disease[14] are covered in other papers in the Series, and will not be covered in this paper. Instead, we focus on the international efforts to build evidence for the optimal return of disease risk genetic variants and use of this data within routine clinical care.

A framework for collecting outcomes and building evidence

Genetic testing is evolving from individual gene or single nucleotide polymorphism variant testing to exome (protein-coding DNA) or genome (almost all DNA) testing, by use of next generation sequencing. The discovery of both rare and common variants has increased exponentially in the past two decades.[15] Although many variants can confidently be designated pathogenic (eg, loss of function *BRCA1* variants), others (such as novel missense variants, or loss of function variants in genes where the disease mechanism does not depend on insufficient protein production such as *PCSK9* and familial hypercholesterolemia) often have uncertain pathogenicity. In fact, only a few novel variants are sufficiently understood, that when incidentally discovered, are considered for reporting to patients. For example, the American College of Medical Genetics and Genomics (ACMG) recommends that pathogenic variants in 59 genes be returned to tested patients regardless of the indication for sequencing.[16] The association between variants within these genes and specific medical conditions in cardiology, oncology, and many other medical specialties are well established and should contribute to individual risk assessments or to justify additional screening (table 1). However, whether returning these variants to individuals or family members improves health is often uncertain, particularly for individuals of average risk before the testing. Complete capture of changes in health delivery and clinical outcomes across a large study population could lead to identification of a vast breadth of genomic conditions. Moreover, important health effects could be latent for decades. Potential outcomes of interest span the individual, their family, and their health-care system. Outcomes in each of these three domains can then be captured across three phases: return of genetic results, the application of

	Associated genes†	Pathogenic variant rate among unselected population‡	Process outcomes	Intermediate outcomes	Clinical outcomes
Hereditary breast and ovarian cancer	*BRCA1, BRCA2*	0·5%[17]	Breast cancer screen modality and schedule	Breast biopsy findings	Prophylactic mastectomy or oophorectomy; diagnosis of breast or ovarian cancer and presenting stage
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*	0·4%	Colorectal cancer screen modality and schedule	Colonoscopy findings, polypectomy	Bilateral salpingo-oophorectomy; incidence and presenting stage of colorectal cancer, ovarian cancer, or endometrial cancer
Familial hypercholesterolaemia	*LDLR, ABOB, PCSK9*	0·4%[18]	Measurement of LDL cholesterol	Initiation or intensification of statin or *PCSK9* inhibitor therapy	Atherosclerotic disease: myocardial infarction, cerebrovascular accident, or peripheral vascular disease
Familial hypertrophic and dilated cardiomyopathy	*TTN, TNNT2, LMNA, MYH7*	0·2%[19,20]	Echocardiogram screening, creatine kinase measurement	Left ventricular wall thickness; implantation of defibrillator or pacemaker	Diagnosis of cardiomyopathy; incidence and presenting stage of congestive heart failure
Familial arrhythmia	*SCN5A, KCNH2, KCNQ1, RYR2*	0·03%§[21]	Electrocardiogram or electrophysiology studies	Medical prophylaxis; defibrillator placement	Incidence of ventricular arrhythmia or sudden death
Hereditary haemochromatosis	*HFE*	0·5%	Ferritin, transferrin saturation measurement	Liver biopsy	Diagnosis of iron overload, cirrhosis, diabetes, or dilated cardiomyopathy

*Subset of returnable conditions. Distinct genes and genomic diagnoses are grouped by related phenotypes. †Partial list of genes associated with condition. ‡Approximate pathogenic and likely pathogenic rate; variant rates vary by ethnicity. §Additional data from the Genome Aggregation Database.

Table 1: **Examples of process, intermediate, and clinical outcomes potentially resulting from sequencing studies by generic syndrome(s)***

the data to clinical decision making, and during longitudinal follow-up (figure). Given that much of genomic medicine will be assessed in the context of large observational studies and implementation strategies, rather than in clinical trials, linking clinical outcomes to the return and application of genetic results will be particularly important to establishing causality. The scope of reportable outcomes will also depend on whether the focus is on a small panel of genes or a larger sequencing effort, such as genome or exome, the timeframe over which outcomes are assessed in sequenced patients, the perspective of the study (societal, health system, or patient-centred) and whether clinical data from family members is sought and captured.

Phases	Individual health domain	Family health domain	Health system domain
Return of results	• Individual understanding • Perception of disease risk • Psychological adjustments • Behavioural changes	• Collection of family health history • Family communication • Family understanding	• Accessibility of results and interpretation • Clinician understanding • Genetic counselling capacity
Application to clinical practice	• Application to risk prediction • Additional screening for genomic diagnosis • Receipt of individualised intervention	• Cascade testing of at-risk family • Screening for genomic diagnoses • Receipt of individualised intervention	• Clinician response to clinical decision support
Longitudinal follow-up	• Diagnosis of individual genomic syndromes • Drug response (pharmacogenomics) • Mortality, morbidity, and quality of life	• Diagnosis of familial genomic syndromes • Reproductive decision making	• Health-care utilisation • Cost-effectiveness

Figure: **Potential outcomes measured within individuals, families, and health systems**

Individual outcomes

Sequencing results could lead to changes in a patient's understanding of genetic findings and clinical risks, anxiety or decisional conflict about the results, changes in health behaviours or lifestyle, and increased information seeking and health care use.[22] Any of these psychological effects or behaviours could have a substantial effect on downstream clinical outcomes. For example, a woman who learns of increased breast cancer risk due to a *BRCA1* gene variant might react by engaging with her health-care provider or a genetic counsellor and follow through with accelerated breast cancer screening or, conversely, avoid additional follow-up due to anxiety or perceived futility of efforts to prevent a poor outcome. Initial reviews of the literature suggested little effect of genetic testing on health behaviours,[23] but later publications suggest that the clinical context, target condition, and aggregation of genetic and non-genetic factors could be important to motivating change.[24,25]

The application of results to clinical risk prediction, additional screening tests, and receipt of individualised intervention are key process outcomes that link return of sequencing results to patients and potential improved health (table 1). Few guidelines exist to help clinicians manage patients with identified genetic risks, but those that are available help to define outcomes of interest through recommendations for additional diagnostic testing, accelerated screening or surveillance schedules for cancer risks, or risk reduction with medical or surgical prophylaxis.[26–32] As an example, the National Comprehensive Cancer Network defines a surveillance strategy of colonoscopy starting at age 20–25 with a repeat every 1–2 years for patients with a known Lynch syndrome related pathogenic variant, and also suggests bilateral salpingo-oophorectomy be considered as a risk-reducing option for women with Lynch syndrome

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

who have completed childbearing.[32] In a cohort study of patients with a variant in one of the Lynch syndrome associated genes (*MLH1, MSH2, MSH6, PMS2*) all of the medical and surgical therapies used to reduce risk should be captured, in addition to tracking the incidence of colorectal, ovarian, endometrial, and other cancers associated with the syndrome.

Family outcomes

One unique feature of genomic medicine studies is the potential for genetic risks identified within an individual (the proband) to affect the care of family members through cascade testing of relatives. Ideally, clinical outcome studies would test first and second degree family members of study participants with a pathogenic variant and track family members (with the consent of the proband and family member) for changes in health-care delivery and clinical outcomes. Given that family members are much more likely than average to also have the variant, cascade testing will increase the efficiency of the study and health effect of the original finding. This increased efficiency has been shown in the context of screening patients with colorectal cancer to identify Lynch Syndrome; cascade testing of relatives before development of cancer was cost-effective.[33] One study showed that as many as 47% of first degree relatives of the proband complete such testing, when cheap and convenient, although other studies show lower uptake.[34,35] In practice, investigators need to plan to overcome logistical and health policy hurdles to cascade testing.[35,36] If successful, the number of patients with a variant of interest to contribute to outcome assessment could nearly double, as was found in a biobank study of Estonian patients with familial hypercholesterolaemia.[37]

Health system outcomes

One of the most important mediators of individual outcomes is the context in which the test results are obtained and applied to clinical care. Testing that is done within an established clinician–patient relationship and in a health-care environment where results are interpreted, and clinical decision support is provided to both patients and clinicians, can have substantially different effect than testing done in other contexts, such as direct-to-consumer or outside a traditional health system. The availability of services, such as genetic counsellors and medical geneticists, could predict improvements in process outcomes such as effective delivery of results and recommendations to patients, but also incur costs to the system in the form of increased health care use, which could reduce overall cost-effectiveness.

Challenges and potential solutions to genomic medicine outcome studies

For more on the **RE-AIM framework** see www.re-aim.org

Building evidence for genomic medicine with outcome-oriented studies involves a host of considerations: the rarity of the returned variants, heterogeneity in minor allele frequencies between different ethnicities, incomplete penetrance, the pleiotropy (ie, heterogeneity) of gene functions, the age of onset of the target conditions, epigenetic effects representing interactions between the environment and gene risks, and differences in disease expression between the sexes, among other issues. These factors suggest large and diverse study populations will be needed to establish the effect of sequencing on human health. Putative pathogenic variant rates for the more common mendelian conditions are present in less than 1% of an unselected population (table 1). Estimates for population-based variant rates across the entire ACMG 59 gene set range from 1–3%.[38–41] A study of 10 000 participants would be expected to yield only 100–300 people with any variant and typically less than 100 participants with a variant associated with a specific phenotype. Therefore, even a large study with thousands of patients would have difficulty discriminating between outcomes in patients with and without a variant or comparing tested and untested populations. Comparative effectiveness research to test a genome informed strategy would also need to account for incomplete penetrance or penetrance that is strongly dependent on age. For example, among patients with multiple endocrine neoplasia type 1 age-related penetrance can vary from 7–10% in the young to nearly complete penetrance by age 60.[42] Unless cohorts are followed up for decades, the ability to detect a phenotype will be strongly affected by the distribution of ages in the study cohort.

Potential solutions

Several authors have pointed out that precision medicine, and genomic medicine in particular, would benefit from a convergence of implementation science and a learning health system to measure outcomes and generate evidence across a large population.[43,44] Implementation science has been defined as "the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services and care".[45] To support outcome evaluation for genomic medicine, the implementation must effectively deliver genetic data to patients and clinicians and provide support for clinical decision making, and the learning health system aspect should capture the process and clinical outcomes during routine clinical care. At least one National Institute of Health (NIH)-funded network is making progress toward this goal. The Implementing Genomics in Practice Network has developed a model and associated demonstration studies to facilitate implementation studies in genomic medicine.[4,46,47] The model's implementation outcomes are based on the principles of the RE-AIM framework: reach, effectiveness, adoption, implementation, and maintenance.[48] Reach describes the target population, including how

generalisable it is, and the uptake of the intervention in that population. Effectiveness addresses the effect of an intervention on important outcomes, including potential negative effects, quality of life, and economic outcomes. Adoption describes the target health setting or provider population and the uptake, implementation describes the cost and the ability to implement the intervention as designed, and maintenance describes the consistency of intervention use over time. To illustrate: if an intervention is completely effective but only reaches a minority of the population or adopted by few providers and poorly sustained, the effect of the intervention will be minimised and create potentially imperceptible health outcome differences.

Methods for capturing outcomes

The need for large studies will necessitate efficient, low-cost strategies for collecting outcomes. Several existing genomic medicine networks have shown the value of electronic health records (EHRs) in aggregating phenotype data across large populations for both discovery and outcomes assessment within a genomic medicine implementation.[5,49] The prospect of using EHRs for population-based outcomes research has improved with broad implementation across many of the countries that are also investing in genomic medicine studies,[50,51] and with the development of public resources such as the Phenotype Knowledge Base to define phenotypes in terms of EHR data algorithms.[52] Sharing of data across diverse clinical environments will also address the challenge of conducting large outcome studies. The introduction of a common computable language to represent coded clinical data and phenotypes (eg, the Observational Medical Outcomes Partnership common data model) is expected to accelerate the trend of merging data across many health systems.[53–57] Although these capabilities are important, additional work is needed to ensure the electronic phenotype algorithms applied to the data in large biobanks or other clinical data repositories are sufficiently validated, reproducible, and specific to the outcomes of interest for genomic medicine.

The state of outcome studies in genomic medicine

The effect of sequencing on clinical outcomes is a subject of active investigation and has led to the establishment of dozens of large cohorts internationally (table 2). These are primarily organised as a prospective cohort or biobank study with the added dimension of return of results planned around the ACMG 59 set of genetic criteria or analogous internally developed criteria. Federally funded consortia (eMERGE III, All of Us, Million Veterans Program) within the US, academic–industry partnerships (Geisinger MyCode Community Health Initiative), and national (UK 100 000 Genomes Project, Estonian Genome Project, Genome Canada) are expected to produce essential information about process and clinical outcomes over time.[37,62,63] Many of these ongoing trials have already begun reporting process outcomes. In a study of 50 000 women assessed for *BRCA* status in the MyCode Community Health Initiative, 75% of carriers of a pathogenic or likely pathogenic *BRCA* variant were not identified as carriers as they had not had clinical testing, and were not therefore receiving recommended care.[17]

Few of the studies we assessed were in the form of a clinical trial. The pilot MedSeq project randomly assigned healthy primary care patients to whole genome sequencing in a primary care setting and found that primary care providers took clinical actions in a third of patients with a medically actionable secondary finding, and that downstream costs did not rise in response.[65,66] Results of MedSeq reported that 2% of tested participants had a mendelian trait linked to a phenotype, but the study was underpowered to measure the penetrance of the variant or changes in clinical outcomes related to the genetic testing.

	Type of genetic data	Source population	Planned enrolment	Enrolment (as of November, 2018)	Genetic and clinical focus of programme
All of Us[58]	Sequencing	USA	1 000 000	76 000	Clinical conditions associated with the ACMG 59* and drug response related to pharmacogenes
Genome Canada[59]	Sequencing	Canada	30 000	0	Rare genetic disease
eMERGE Network (3rd round)[5]	Targeted sequencing	USA based health-care network	25 000	25 000	Clinical conditions associated with the ACMG 59*
Estonian Genome Project[37,60]	Genotyping	Estonia	150 000	52 000	Rare genetic disease and familial hyperlipidaemia
Geisinger MyCode Community Health Initiative[61,62]	Exome sequencing	USA based integrated health system	500 000	225 000	Clinical conditions associated with a Geisinger defined gene list
UK 100 000 Genomes Project[63]†	Whole genome sequencing	UK	100 000	87 231	Rare genetic disease and cancer

eMERGE=Electronic Medical Records and Genomics. *ACMG 59 is a list of genes curated by the American College of Medical Genetics that are returnable in the context of sequencing regardless of the indication for testing. †Expansion announced.

Table 2: **Selected large cohort studies that return results to participants and conduct longitudinal follow-up**

Implications of outcome research

As the use of next generation sequencing technologies in genomic medicine increases, patients in various clinical contexts are likely to be recipients of genetic findings that were not related to the indication for testing. Clinical outcome studies in these patients is crucially important to developing evidence-based policies around the return of secondary findings and guidelines for genome-informed care. Although randomised clinical trials would provide the strongest evidence for clinical benefits or harms for returning specific types of variants, the uncommon frequency and latency of genetic variation strongly associated with disease make such trials expensive, impractical, or pre-empted by compelling observational data. We anticipate that large cohort studies that return results to participants and follow up participants over time will gradually inform the use of sequencing results in clinical practice, but this process could take decades to complete, particularly for conditions associated with rare variation. Several steps can be taken to accelerate such studies and dissemination of the findings. As yet, there are no standard outcome measures for cross-study use, but collaboration and interchange between NIH consortia are beginning to define common methods.[67] Standard outcome approaches will enable the aggregation of outcome data across different study populations, a feature that could overcome the inherent need for ever larger study populations to assess penetrance in rare variants and the associated change in clinical outcomes. Development of publicly available, standardised outcome measures can rapidly expand knowledge, as shown by the Patient-Reported Outcome measures, initially developed with NIH funding and now in broad use for research and increasingly in clinical care.[68] Secondly, offering cascade testing to families of proband study participants will increase the efficiency of identifying carriers; if these family members are also followed up clinically, the pace of determining outcomes will be greatly amplified. Finally, national and international consortia, similar to the ClinVar and Clinical Genome Resource (ClinGen),[69–71] could accumulate evidence-based algorithms for managing secondary findings, just as existing resources catalogue the clinical relevance of genes and variants.

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

Reporting how individual and family health is improved by return of sequencing results will help address several of the barriers to genomic medicine adoption. Adoption of genomic medicine is limited by clinical inertia and inadequate strategies for accelerating clinical practice guideline adherence in instances where definitive diagnosis and treatment are available. For example, nearly half of patients with familial hypercholesterolaemia do not receive the recommended treatment, and less than a quarter of patients eligible for high-intensity statin treatment receive it or achieve treatment targets.[72]

Across all study types, study investigators need to be alert to potential bias and limitations. Clinical outcomes could be markedly influenced by selection biases. Study cohorts that accumulate patients with specific phenotypes (eg, an existing diagnosis of cancer or rare disease) will have an ascertainment bias that will not be correctable during analyses. Secondly, the age at enrolment of study participants could strongly affect outcome assessments; for example, an older study cohort might obscure increased mortality at younger ages due to survival bias. Thirdly, the need for observational, non-randomised study designs to satisfy large recruitment requirements could increase the effect of confounding on the evidence base for the field. Finally, it might be difficult to conclude that the outcome is attributable to the genomic result; for example, was a mammogram on a woman after the return of a genomic result done in response to the result, or as part of regularly scheduled preventive care? Although some interventions can be confidently attributed to the return of the results based on timing and rarity of the test in routine care (eg, serum ammonia concentration after return of a pathogenic variant in ornithine transcarbamylase) others (such as the mammogram example) warrant more discretion to avoid confounding. As the discovery of rare variants with predicted pathogenicity accelerates, the risk of false positive and false negative outcome associations increases.

The practice of genomic medicine is expected to expand from the identification and care of patients with single-gene mendelian disorders to more common conditions with complex genetic associations. The development of polygenic risk scores to predict the onset of cardiovascular disease in adult patients is an extant example.[73,74] As these disorders have multifaceted causes with established clinical risks, high dimensional genomic risks involving thousands or millions of variants, and potential epigenetic risks, outcome evaluations will need to compare clinical to clinical genomic strategies at a scale that can differentiate the incremental benefit of adding genomic data to a standard clinical risk model.

Conclusion

Building evidence for genomic sequencing to individualise preventive care strategies, improve early diagnosis of genomic syndromes, and to tailor therapeutic plans will require an extensive international effort to recruit and follow up large and diverse study populations for clinical outcomes. Increased emphasis on implementation research will help achieve the necessary scale and identify sustainable strategies for accelerating the adoption of guideline-recommended practices.

Contributors

DMR, LAO, AHR, GAM, and MSW contributed to manuscript organisation, scope, editing of the initial draft, and revision. JFP generated the initial draft and contributed to revision.

Declaration of interests

JFP is a consultant for Color Genomics outside the submitted work. MSW reports grants from National Human Genome Institute, National Institutes of Health, during the conduct of the study. All other authors declare no competing interests.

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