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Genomic Medicine XV: Genomics and Population Screening
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Meeting Summary

Welcome, Introductions, and Goals

The Genomic Medicine Working Group (GMWG) convened leaders in genomic medicine to discuss the current state of population genomic screening in the U.S., as well as barriers and opportunities for expanded population screening, impact on clinical practice and outcomes, various genomic screening technologies and costs, and evidence gaps that may inform future research directions.

The meeting opened with a brief overview of past Genomic Medicine meetings and resulting programs and initiatives that have evolved from them, as well as the charge of the GMWG. In addition to the items called out in the agenda, the meeting covered the role of geneticists and genetic counselors in population screening, the potential role of telehealth and AI, the importance of keeping approaches/guidelines simple and engaging with health systems' leadership, the risks of and dealing with false positives, and research needed so that the healthcare system would be ready to handle population screening. Items that were not to be addressed included newborn screening (NBS) and screening of children under 18, appropriateness of potential intervention once a condition is found, and funding opportunities or mechanisms.

The objectives for this meeting included:

- Review the current state of population genomic screening in the U.S.,
- Examine obstacles and opportunities for expanded screening and available evidence of the impact of screening on outcomes and cost,
- Identify research directions to inform expanded screening as appropriate.

Session 1: Laying the Groundwork

The central theme for the first keynote was that "genomics is not exceptional." Genomic testing performs like every other medical test: it has sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and the PPV depends on the testing scenario. What may be exceptional about genomics, however, is genetics *practice*. Generally, clinical genomic testing is used in scenarios where *prior probability* of disease is high. When shifting to population screening, the prior probability plummets. Thus, a formal, probabilistic model of genetic diagnosis for population screening is needed. Diseases such as hereditary cancers, genetic diseases, and birth defects are thought of as deterministic, but they are still probabilistic—they have an increased susceptibility to an abnormal phenotype, but the penetrance function is essentially 100%. Nearly all variants have a probability of pathogenicity rather than being certain to be causative—the diagnosis of the patient depends on the prior probability of disease. A stepwise, systematic approach would assess probability of pathogenicity of the variant, and then of having the phenotype given the presence of a pathogenic variant (penetrance). Test results, prior history of disease, and family health history can all impact risk—for hereditary breast and ovarian cancer syndrome (HBOC) pathogenic variants, for example, the lifetime risk can vary widely among individuals. To create a probabilistic model, robust variant classification is needed to determine pathogenicity, as are practical methods for detecting one or more relevant phenotypes. This necessitates decision-making support for patients, as well as defined care pathways and clinical decision support (CDS). The larger

challenge is to move from diagnosis-based to preventive health—motivating people who don't have the manifestations of the disease to engage in desired health behaviors.

The second keynote opened with the supposition that eventually, every individual will have a comprehensive genomic dataset generated in the newborn period and linked to the electronic health record (EHR) used throughout their lives in two ways: for reiterative population screening and for a clinically indicated diagnostic assessment. Primary findings are screening results generated from data sets created for genomic screening, as opposed to secondary findings, which are generated by analyzing data sets created for a primary purpose other than screening (such as diagnosis of a specific disease).

Screening for disease differs from screening for *risk* of disease: in the former, the goal is treatment; in the latter, it is prevention and early diagnosis. For risk screening, there is no symptom that drives evaluation. The genetic test is the start of the journey, with some findings leading to diagnosis (and treatment) and others being re-evaluated periodically. In every screening situation, there will be those with a genotype only, without the disease. While people are understandably cautious about returning risk results if the patient may not get the disease, this occurs frequently in healthcare—for example, recommending smoking cessation to reduce risk of heart disease or cancer. Not every smoker will get heart disease or cancer, but it still makes sense to reduce risk by not smoking. Non-penetrant risk does not necessarily run in families, so cascade testing and evidence development around non-penetrant risk may be useful.

Currently recommended strategies for screening include screening for HBOC pathogenic variants if there is a personal or family history of breast, ovarian, tubal, or peritoneal cancer, or an ancestry associated with the *BRCA1/2* variants and a high-risk family history. However, with this strategy, 4 out of 10 adults with pathogenic or likely pathogenic HBOC variants would not meet the criteria for screening. Additionally, about 27,000 volunteers from the Healthy Nevada Project underwent DNA-based screening for HBOC, Lynch syndrome, and familial hypercholesterolemia (FH)—the 2012 CDC Tier 1 conditions—and 90% of those identified as at risk were unaware of their genetic risk.

A strategy that includes the CDC Tier 1 conditions is likely the starting point for population screening Which, if any, additional genes and conditions should be included is currently unclear, but clinical utility—the effective access to appropriate interventions that result in an improved health outcome—should be the primary driver. Researchers should consult engaged populations and experts whose preferences could drive considerations.

Current evidence is insufficient to support routine implementation of genomic screening. It may be worth creating a timeline with milestones as a roadmap to implementation. Current population screening projects are privately funded research efforts. There need to be rules, regulations, and penalties around the use and misuse of data. People owning their own genomic dataset could be viewed as a public good.

Session 1: Discussion

Secondary findings in somatic tumor testing can be challenging as somatic testing lowers the analytic validity of a finding relevant to the germline. Many patients subsequently have reflex germline testing so this lands somewhere between population and opportunistic screening.

A probabilistic model for conditions to be screened could lead to something similar to the Richards criteria for variant interpretation, which would explicitly lay out what information needs to be generated.

What types of errors can be tolerated needs consideration. Even Tier 1 conditions differ—a false positive for HBOC could result in unnecessary surgery, while the outcomes are less drastic for false positive FH

and clinical biomarkers are available (such as LDL-C) that supplement the genomic result. Evidence is needed to move conditions into the "Tier 1" level; current estimates of disease risk over a lifetime are not based on screening data but rather on clinical data; better numbers are needed. It may take several decades, although some places like Geisinger already have about 10 years' worth of experience.

Research utility can be a motivating factor for patients, providers, and leadership. This is synergistic with GM XIV, which discussed genomic learning health systems (gLHS). gLHS integrate research and clinical practice and allow patients and providers to see the clinical benefit of their participation in research.

A challenging issue is that different patients will have different priorities. This usually falls within the purview of genetic counselors (GCs) at present, but the current GC workforce is inadequate to deal with clinical testing, let alone population screening. The hour-long GC encounter must change into something that's scalable, perhaps through broadly available online interactive tools that can accommodate patient preferences.

It is difficult to get people to change health behaviors. The process must be as simple and automated as possible. However, genetic test results seem to have more of an effect in terms of health behaviors than other recommendations based on publication of some initial outcomes analyses. They may also generate more uncertainty and may cause harm.

Session 2: Genomic Screening Technologies

An overview of the current state of clinical methods for population genomic screening included the importance of optimizing high throughput genomic screening to ensure consistent DNA source and quality, use automated workflows, ensure stable process for library automation, be cost efficient, continually upgrade laboratory processes and software, define metrics to monitor production quality, leverage semi-automated analysis pipelines, and maintain clear communication of reporting practices.

For a clinical next-generation sequencing (NGS) test, there are three general stages of validation: test development and optimization, test validation, and test performance monitoring or quality management. Quality metrics and periodic review of positivity rates are essential to ensure that positives are being captured while not overreporting. Sample collection options range from non-invasive (saliva) to more invasive (whole blood), and consideration must be given to participant convenience, bullet-proof labeling and downstream matching to contact information, cost, automation potential, sample stability, failure rate, and long-term storage. Choice of platform for high throughput testing is important, whether genotyping array, targeted NGS panel, whole exome sequencing, whole genome sequencing, or a hybrid design. Result parameters need to be clearly communicated to providers and participants. Re-contact and re-analysis expectations need to be defined in advance.

Though there are clear distinctions between the reporting of diagnostic and screening genomic tests, the associated laboratory quality measures are not distinct. This can impose challenges on laboratories due to the high throughput nature of screening tests. Scientists must be prudent when adding new approaches to existing workflows or launching new tests, as each requires continual testing, validation, and monitoring. Test validation must be extremely thorough, as weaknesses will be exposed with high throughput testing.

Lessons learned from newborn screening (NBS) can be applied to screening for adult populations. NBS is already the largest genetic screening program in the country, with 4 million newborns screened per year. The newborn period is a unique opportunity to intervene in serious, urgent, and treatable disorders before symptoms develop. As this is largely a public health-driven process rather than one opted for by parents, the state must be a trusted partner and use screening tests with a low false positive rate and high PPV.

Secondary sequencing is a powerful method for resolving false positive results and for defining the diagnosis when NBS implicates multiple disorders.

Sensitivity and specificity are challenges for primary population screening. Compared to current NBS, adult genomic sequencing is more expensive and suffers from reduced analytical and clinical sensitivity and specificity due to variants of uncertain significance (VUS). Disparities in variant interpretation for individuals from ancestries underrepresented in genomics databases also exacerbate racial and ethnic disparities. Primary sequencing holds promise for NBS for disorders without an available biomarker.

Areas for future work include screening tests that distinguish early- from late-onset forms of disease, diagnostic testing following screening, sharing variant data from screening results, interpreting compound heterozygotes, pre-symptomatic clinical management, and disease characteristics in diverse populations.

Another approach to genomic screening is to calculate the "number needed to screen." In simulating fixed monogenic disease prevalence and tunable test performance, one can predict the rate of true positives, false positives, false negatives, true negatives, sensitivity, and specificity. The number needed to diagnose one true positive depends on characteristics of both test and disease. For monogenic diseases, critical values for the "number needed" include prevalence, screening test performance, and penetrance.

The threshold that qualifies for a "positive" screen can be tuned based on the condition, the PPV, the ability to reduce false positives and mitigate overdiagnosis, and the management recommended for those with positive screening results. Incorporation into cost effectiveness analyses is still needed.

Session 2: Discussion

Genomic screening technologies pose many areas for future research. Development of recommendations for sample collection and reanalysis of variants would be useful as would better estimates of the prevalence of monogenic diseases, natural history, and age-related prevalence.

We need to determine the best method to hand off positive genetic test results to clinical providers, and whether that should be primary care providers (PCPs), specialists, or other groups. Long-term follow-up remains a challenge. Potential harms of reporting and treating false positives should be recognized. In this vein, the "disutility" or "number to harm" should be carefully considered when tuning screening results.

Implications of negative test results need to be understood, including how patients interpret negative tests and what genetic counseling and follow-up are needed. Patients with a clear phenotype and negative genetic testing still need follow-up, but those with no phenotype may not need genetic counseling or follow-up. Communication of negative results remains a question, as automated technology like chatbots may be a non-inferior option. PCPs may also use negative screening as a teachable moment.

There is substantial inequity in variant interpretation due to lack of genomic data from underrepresented groups. Though several projects are working to increase representation of diverse ancestries, the work is not yet at the point for population screening to maximize true positives and minimize false positives and negatives for all people. Widespread models to support data sharing will be important to achieve this goal.

MaveDB, the Impact of Genomic Variant on Function (IGVF) program, and similar basic science efforts develop and perform high throughput functional assays. Engagement among these groups, ClinGen, and ACMG has potential to focus knowledge for genes and variants ready for population-based screening.

Session 3: Logistics of population screening

PCPs order non-genetic tests without referral and may then refer to appropriate specialists; genetic tests should work similarly. Additionally, the single-test model—performing genomic testing at birth and reanalyzing the data across the lifespan—lends itself to primary care, given that primary care comprises the lifetime patient relationship. Reanalysis can then occur at the appropriate times. Genetic results should go to PCPs, who are the "first line" for medical care, have the lowest access barriers, implement preventive care, and whose scope of practice already aligns with genomic screening. The primary care workforce is not ready yet, but they can and should work towards this. Critical needs include efficiency measures, knowledge, confidence, and a robust informatics infrastructure to support reanalysis. These can be facilitated by just-in-time CDS and other informatics support, defining the "minimum viable product" for management, and informed consent as needed. Integration into the health care record necessitates better EHR systems. In the primary care space, genetics should be implemented gradually, picking one high-value, high-evidence screening test and adopting more when successful.

Mammography screening for breast cancer is a successful non-genetic screening model, with people at higher- and lower-risk identifiable by genetic testing. Current practice for CDC Tier 1 conditions starts with testing based on personal and family history. Patients who have a moderate risk or an uninformative result may be further risk stratified by polygenic risk scores (PRS). There are also people with variants that are not yet classifiable; potentially testing could be automated to identify those who should be screened. General screening may be more effective at bringing in more people, especially among underrepresented populations. Those who would have not been identified under current guidelines would be identified in a population screening program. A simulated model showed that population screening was able to prevent cases of cancer or deaths from cardiovascular disease. The age at which screening started affected effectiveness, with starting at age 30 as the most effective. However, there are still significant gaps in coverage and barriers related to cost, transportation, burden on healthcare systems, and subsequent follow up. In the paper "Sick Individuals and Sick Populations," Geoffrey Rose outlined two strategies for lowering the burden of disease: the high-risk strategy, where one identifies patients at a higher risk and intervenes early, and the population approach, aiming to shift the underlying risk of the overall population. The former has a potentially large impact on a small population, while the latter there would have a large population impact but the difference for any one individual would be small. It is likely that a combination of approaches will be required to efficiently improve population health and narrow health disparities.

Self-reported race and ethnicity do not capture the true genetic diversity of the U.S. Identity is multi-dimensional and involves ancestry, genetic lineage, genealogy, and cultural practice. Race and ethnicity are constructs; using these terms interchangeably with genetic ancestry can lead to inaccuracy, and they can also change over time and across different social contexts. Though progress has been made, most large genomic studies and databases are heavily weighted towards those with a European ancestry, which limits diversity. That lack of representation increases the risk of perpetuating and exacerbating health disparities. A lack of diversity of participants in genetic and genomic studies leads to limited progress in understanding genetic determinants of health disparities by race and ethnicity across the lifespan.

Traditional reproductive carrier screening was often based on ancestry but as such missed people who may be at risk. For example, newborns with sickle cell disease are not exclusively identified as African-American, but this is the population that was targeted for carrier screening. The current expanded carrier screening approach captures the entire population in a pan-ethnic way. This led to improved guidelines, such as screening all pregnant patients for conditions with carrier frequency $\geq$ to 1 in 200.

Yet there are challenges—in many carrier screening studies there are small percentages of participants with non-European ancestry. Additionally, patients who are non-White typically have a harder time accessing care due to cost and other factors. Provider bias and discrimination also impact patients—non-White patients are less likely to get a genetic evaluation or referral, or be offered tests, nor may they be inclined to access care because of prior perceived discrimination and poor treatment. Engaging individuals, families, and communities; educating healthcare providers; building trust; and making sure patients have access to culturally sensitive and affordable patient care are essential to capturing the diversity and making genomic medicine equitable for all.

Valuable lessons have been learned from several initiatives in Alabama: Information Is Power (IIP), the Alabama Genomic Health Initiative (AGHI), and SouthSeq. The first is a cancer risk gene panel for adults in Alabama. The tests are consumer-directed and physician-ordered with over 6,500 participants. The AGHI is a research study looking at array-based tests for actionable disease risk and pharmacogenomics for adults in Alabama. SouthSeq is a study of WGS for affected infants in NICUs at five sites.

Population screening will identify many people with unmet needs for diagnostic testing. Almost half of AGHI and IIP participants had a positive family history where further action was needed regardless of test results. Personal and/or family history often does not corroborate positive genetic screening results; in AGHI, only 36% with a positive disease risk had a corresponding personal or family history. Patients and providers often overinterpret negative or uninformative results, leading to false reassurance. In SouthSeq, non-genetic providers were more likely than GCs to overinterpret negative results, omit critical details, and/or misquote recurrence risk. The benefits of screening extend beyond the patient being tested to risk assessment of relatives. Integration with clinical care seems to improve access to screening and follow-up but this may also create barriers for people who don’t have a PCP, and providers still need education, training, and infrastructure to help providers facilitate care.

Session 3: Discussion

Potential projects proposed by speakers including use of CDS in the primary care space, as it will be difficult to adopt genetics into primary care without these tools. End-user experience is critical; PCPs are currently overwhelmed with interruptive CDS alerts that often get ignored. A major point of discussion was whom to engage in integrating genomics into practice: PCPs or specialists? Several speakers felt that they had a difficult time engaging PCPs and that specialty care providers might be more receptive, but there are even greater barriers in accessing specialists. Reaching out to PCPs with the principles of meaningful community engagement to develop co-created solutions might be the path forward. Working on collaborative care models to give PCPs confidence in their genomics knowledge could be another step. Having more robust and ongoing genetics and genomics education in residency programs and medical school would help integrate genomics as part of primary care. It may be worth having a meeting where genomic and PCP leaders share perspectives and the weights they place on the emerging evidence.

Inclusion of conditions of importance to particular groups could be a vehicle for community engagement and used to start conversations around screening for other conditions. That could help to build trust and expand screening opportunities, but there should be a contact in the community who already has that trust.

Most patients talk to their relatives about their genetic results so developing resources with information on their risk and next steps can help patients. However, there is still low uptake of cascade screening. Population screening eliminates cascade screening and lifts that burden from patients and providers.

Session 4: Community Engagement and Population Genomic Screening

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There is much to learn about meaningful community engagement with American Indian/Alaska Native (AI/AN) populations and other marginalized communities. Today, there are 574 federally recognized AI/AN Tribes in 37 states, making up a population of 5.2 million individuals. AI/AN populations have long experienced lower health status compared to other Americans. AI/AN tribes are sovereign nations with an inherent right to self-determination, including deciding how health research may be conducted.

Community engagement can be defined as the process of working collaboratively with a community to address issues that impact the well-being of the group. This entails proactively seeking out community values, concerns, and aspirations, then incorporating those into decision-making and establishing ongoing partnership. Arnstein's "Ladder of Citizen Participation" is a guide to understand who has power in decision-making, with rungs ranging from manipulation (low) to consultation to citizen control (high). Proper community engagement requires collaborative planning and active participation during all phases of research, from conceptualization to dissemination. Researchers must respect sovereignty and self-determination, acknowledge harms, and follow the lead of the community.

Even with the expanded ACMG panel, only 5 medically actionable genes have variant information specific to AI/AN individuals, who constitute <1% of research participants. This is not simply a matter of engagement via recruitment nor selling the benefits of genomic medicine, but overcoming mistrust, thinking proximally about health, and empowering data-decision equity. Disengagement of Indigenous people from genomic research can be attributed to structural inequities in health care funding as well as a cycle of victim-blaming and coercion propagated from power imbalances that create research harms.

The clinical pathway of care for rural, tribal patients seeking genetic testing is burdensome. It poses questions about culturally specific care, data sharing, and privacy laws. Indigenous patients derive little to no clinical utility due to the lack of informative variants specific to them. Additionally, providers may not be aware that commercial genetic testing companies can co-opt and claim ownership of Indigenous peoples' genomic data and deposit them into public databases, yet such companies have been unwilling to use these data to create therapeutics that specifically impact these groups. The health inequity problem will not be solved by recruiting more Indigenous peoples into data sets nor allocating genetic tests in their communities. Indigenous people are concerned about the unconsented use of their data in other studies. Digital data tools may help facilitate data sharing and respect Indigenous genomic data sovereignty.

Colonial definitions of Indigeneity and using Indigeneity as a biological construct should be avoided. Indigenous populations are not stagnant, and the focus on "least admixed" peoples ignores the lived experiences of many. The shift from genetic ancestry to genetic similarity is appropriate.

The *All of Us (AoU)* Research Program was launched in 2019 to accelerate health research and medical breakthroughs. Though not solely genomics-focused, it is one of the most diverse genomic studies to date. Over 80% of participants self-identify as coming from underrepresented communities in biomedical research, defined by age, race, ethnicity, geography, disability, sexual orientation, and gender identity.

AoU funded community engagement partners before participant enrollment began and has continued to expand its engagement ecosystem. Their engagement framework begins with outreach and awareness, fosters education and access, continues engagement activities to enroll and retain, integrates participants as partners, and finally mobilizes knowledge. It is best practice to include partners "at the table," both as trusted messengers to their communities but also as co-developers programmatically. One example is working with PRIDEnet and the American Association on Health and Disability to co-develop survey questions that address critical missing data or communication materials that are inclusive at all levels.

AoU began returning health-related DNA results to participants in December 2022 and recently began offering genetic ancestry and traits, hereditary disease risk based on the ACMG panel of 59 genes, and 7 genes associated with pharmacogenomics. An estimated 2.9% of consenting participants may receive pathogenic or likely pathogenic results. The program provides clinical validation testing for pathogenic and likely pathogenic results based on listening sessions with participant ambassadors. All participants have access to genetic counseling and interpreter services. The AoU platform was designed for a community of diverse researchers to use the data; this is achieved through a number of different researcher engagement strategies.

Panel: Selecting Conditions for Screening

The Medical University of South Carolina implemented a population-wide genomic screening program in 2021 that provides whole-genome sequencing and aims to enroll 100,000 adults. It returns Tier 1 conditions because they are well-vetted, considered actionable, and positive and negative findings can be clearly explained. Downstream clinical outcomes are being tracked. Areas for future expansion include pediatric populations, pharmacogenomics, and secondary findings.

Evidence-based methods were developed and used to produce recommendations for genetic screening on a population level but these methods have remained unchanged for over 12 years. It is critical to understand what evidence is needed to expand the Tier 1 list by identifying genetic tests that are almost ready and the gaps to be filled to make them "bullet proof." One approach is to fund health systems to pilot almost-ready tests, but these systems do not serve all communities and so may exacerbate inequities.

Community engagement has been valuable to ensure reports are inclusive and that measures reflect what researchers and patients are looking for. The NIH Office of Disease Prevention works to stimulate prevention research and identify key gaps. Of all NIH prevention research, a third looks at leading risk-factors, with only a small sliver working with health disparity populations. There was agreement that systematic community advisory boards with diverse representation and lived experiences are essential to tailor delivery of a program. Patients must be engaged at every step of the process as true co-creators.

Session 4: Discussion

To improve engagement and identify medically actionable genes for tribal communities, researchers must consider specific tests, validation, return of results, discrimination, and data harmonization. The policies and governing agencies for research and public health differ in terms of ethics, regulations, and sanctions. IRB mandates also impose challenges as not all tribes have an IRB and those who do still are subject to universities' institutional policies. There is thus a distinction between respecting and operationalizing indigenous sovereignty. Blockchain infrastructure and dynamic consenting models may be a way for people to control their genomic data. Both individual and tribal levels of controlled access are possible.

There are additional considerations for other marginalized communities who do not have organized structures for consultation. These include who comprises the community and how engagement is to be done to avoid tokenism and ensure just distribution of benefits. Universal principles such as respect and humility should be extended to global thinking. From a research perspective, measures of trust are important. Trust might be assessed by determining researcher engagement in community-led processes such as pre-approval of a concept, tracking research dollars, or promises of researchers.

Only half of AoU participants opted in to receiving hereditary disease risk information and pharmacogenomics results, though only 73% have actually reviewed the results to date. AoU is investigating why these proportions are not higher and what could/should be done to address the issue.

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Session 5: Evidence needed to support screening

Value in healthcare is the "measured improvement in a person's health outcomes for the cost of achieving that improvement." The best value would be that health outcomes improve while cost decreases; immunizations are an example of these. There are cases where health outcomes are worth increased cost, as in molecularly-targeted cancer treatments; there are also, unfortunately, cases where outcomes worsen while the cost of care increases, as in bone marrow transplants for advanced breast cancer. Health outcomes involve the change in the health of the individual, group, or population attributable to an intervention, but the challenge is that it may take months or years to detect these changes.

The goal of value-based care is to enable the healthcare system to create more value for patients. This is not the same as quality or patient satisfaction but does include both. Understanding healthcare from the patient perspective enables implementation of solutions that enhance value from the patient perspective.

MyCode and the Rational Integration of Clinical Sequencing (RISE) study undertook population screening for CDC Tier 1 conditions and assessed value-based healthcare. In MyCode, most patients were unaware of their Tier 1 variant and eligible to perform risk management. 68% performed management post-disclosure and a diagnosis was made in 13% of patients. The RISE study showed there was cost effectiveness when screening all three Tier 1 conditions (together) before the age of 40.

Standardizing or harmonizing outcomes has been done in eMERGE III and the ClinGen Actionability WG, which compared eMERGE health outcomes to ClinGen's outcome/intervention pairs and identified concordance and discordance. CSER2 sites harmonized clinical outcomes, healthcare utilization, and health economics, as well as engaging with payers and policymakers to collect outcomes of interest.

The RISE study looked at cost-effectiveness of population screening for the three Tier 1 conditions. They modeled population screening against testing stimulated by family history and assigned probabilities such as whether the patient received screening, whether a pathogenic variant was found, whether a variant carrier was affected, and whether appropriate actions were taken after screening. Confirmatory testing is needed, especially for conditions needing significant medical interventions, but does not add significantly to cost as it's done in a small fraction of the population, yet the cost is spread over the entire population.

The authors also modeled levels of uptake of risk-reducing interventions and cascade testing. It is not cost-effective to screen Tier 1 conditions individually (excepting screening for *BRCA1/2* in young women), but when all three conditions are screened for together it becomes cost-effective, especially when screening starts in a younger population (adults aged 20-40). Cost-effectiveness can be lost, however; if 50% decrease in follow-up occurs, for example, and if false reassurance means that people avoid routine disease screening, the overall benefit of screening could be lost. Preliminary work in PRS suggests it's unlikely to be cost effective.

Implications include that prevalence drives economic value so screening should include the most prevalent conditions and combine conditions. Clinical action is required for traditional economic value so the focus should be on clinical actionability. Screening should also be efficient and relatively inexpensive.

In summary, population screening for CDC Tier 1 conditions provides an excellent starting place for population genomic screening as it likely has a positive risk-benefit profile and provides good economic value. Further research is needed on behavior of those with and without a variant, evidence for underserved populations, and implementation outcomes. Combining conditions is essential for economic value and focusing on conditions with clinical or patient-centered value is critical. Genomic population screening applications will vary dramatically in their economic value and evidence requirements.

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The Alabama Genomic Health Initiative (AGHI) is a research study looking at array-based tests for actionable disease risk and pharmacogenomics for adults in Alabama. Participants had a genotyping array done and actionable variants were returned, with genetic counseling and introduction to supportive care. Original demographics were heavily weighted towards those with European ancestry.

In terms of motivation, two-thirds of participants claimed to be interested in contributing to research, and almost as many were concerned about a future health problem. Some were simply curious; many were interested in what this could mean for their family, while others used it to fill the gap if they did not have information about their family health history. One motivation that was concerning was the perception that AGHI would provide access to testing that insurance wouldn't pay even though the AGHI emphasized that it did not substitute for clinical testing. Given the limitations, this could have led to false reassurance.

AGHI also set up a community advisory board that met on topics to help with sensitivity to community needs. Before and after the meetings, the board was surveyed on its attitudes towards genomic medicine. There was little change in the assumption that unnecessary medical tests would be done, and the board felt AGHI would give individuals have more control over their health. Physicians' attitudes towards genomic medicine were slightly but not strongly positive; implementation outcomes were also modestly positive. Benefits included helping patients be more proactive in their health and focusing on prevention and customized prescribing; patient reactions were mostly positive. Implementation requires support and integration into the normal clinical workflow to gain acceptance among providers.

While 13% of the U.S. population is Black, 35% of the U.S. population on dialysis is Black. Early on, blame for poor adherence to medical interventions was assigned to the patient; now, it is clearer that bias is extensive in medical care and affects outcomes. Social determinants of health also impact outcomes; for example, exposure to air pollution, which disproportionately affects Black populations due to residential segregation, is strongly related to kidney disease in those with high-risk *APOL1* variants. *APOL1* risk variants are common and increase lifetime risk of end-stage kidney disease by up to tenfold. The variants are disproportionately common among those with African ancestry (1 in 7 who self-identify as Black) and are otherwise quite rare. Representatives of the Black community were strongly in favor of research in this area—they had been told their high rates of kidney disease were due to "bad behavior" on their part but the research shows otherwise. Targeted screening for *APOL1* makes sense given that the gene originated in West Africa. There are some diseases where it is clear that there is a strong correlation (e.g., HIV associated nephropathy in Africa), and others where it is clear that there is no correlation (e.g., diabetic nephropathy). However, research needs to be done where there isn't as much certainty, such as nondiabetic CKD, particularly those with hypertension and early kidney disease. One example of this is Nadkarni et al.'s primary care pragmatic trial, where patients were randomized into receiving immediate vs. delayed care. There was strong community engagement; over 2000 patients who self-report as having African ancestry were enrolled in 15 sites across NYC. Genetic counselors trained staff from the community who returned results; patients were offered genetic counseling and providers got best practice alerts in the EHR. Blood pressure decreased and CKD screening increased in *APOL1* positive patients.

Translation is a team venture; an accelerator model brings together patient advocates, clinicians, researchers, funders, public health workers, and those in industry to come up with new designs and processes from inception. Not all disparities are prompted by genetics; it is still important to look at their causes. Additionally, most patients do change behaviors, are less concerned about insurance, and are generally more positive than clinicians generally think. There is the ongoing idea that patients mistrust clinicians, especially when it comes to genomic testing—but perhaps it's the other way around.

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Session 5: Discussion

If *APOL1* was part of a general population screening panel, barriers would include need for consent, accessible information for patients, and best practice alerts for providers, as well as reimbursement options. Additionally, there are cases where a positive *APOL1* variant doesn't necessarily increase disease risk, as is the case with people with diabetes, for example.

While it seems that the earlier the better when it comes to screening, this may lead to over-screening. Generating a sequence at birth is likely the most pragmatic, but enrolling healthy year-old babies has also proved successful. This doesn't necessarily mean that newborn *screening* is being done—rather, that sequence has been generated that can also be used as a reference for indication-based testing over a lifetime. Certain interventions when doing NBS need to be done quickly, but rapid NICU genomic analysis is costly. Therefore, another potential time point is the prenatal period, where there is a several-month period to think about findings, although carrier screening should likely be done before conception. Genomic screening could also be done later in life—for example, at eighteen when registering to vote. This model would fall outside of the healthcare system and might be interesting to explore.

Until sequencing technology improves, there may only be opportunistic reanalysis; doing another diagnostic test would likely require resequencing. Another option for lifetime testing might include a series of panels throughout the lifespan for relevant conditions at appropriate times. Regardless, there's a missed opportunity with sequences that are discarded as there is still information that could have been used over many subsequent years. Individuals are unlikely to live out their entire life in the health system that they started in; the genome could be stored in an integrated health system, but in a non-integrated health system, an alternate solution—such as genomic data "banks"—would need to be created. The data have to move with the patient as the patient moves through the health system.

Usually, there's no consent process for ordering non-genetic tests in the clinic. However, there are situations where a physician might order a test and not know what to do with the results, especially in cases of variants of unknown significance. Additionally, states have different laws that apply to genetic and genomic testing. A tiered approach might work; for example, PGx testing might have a lower bar and may not need a discussion around consent, but for variant detection that may lead to life-altering surgeries, the process might be different. Coming up with the "minimum standard" of consent– the critical elements of consent that are universal—and standardizing those would be useful.

Risk stratification might enable implementing a less intense screening approach for certain lower-risk populations that could improve cost-effectiveness. However, this might result in people with lower risk of disease not adhering to population-based recommendations, which might lead to poorer outcomes. In terms of PRS, a higher the risk threshold used to alert a patient of increased risk would reduce false positives at the risk of also reducing true positives. The risk threshold that was used in eMERGE was 2-10%, varying with condition. If PRS are combined across conditions, there may be additional value.

There are several ways to fill evidence gaps in terms of Tier 1 conditions. The most obvious would be to get more tests to meet Tier 1 criteria, as by implementing the Tier 1 conditions and adding "provisional studies" to generate evidence. A risk-based approach could also be taken, understanding what the risks of modifying the clinical benefit or economic value are, rather than trying to meet the bar of Tier 1 screening. Hemochromatosis and hypertrophic cardiomyopathy are both possible targets for next steps.

Session 6: Obstacles to Screening

From a payer perspective, there are multiple reasons to be reluctant to cover genetic screening tests. Issues weighing heavily in payers' decision-making processes include the cost effectiveness and up-front risk of the screening, the lack of strong evidence supporting both the screening performance to identify high-risk patients and the positive outcomes of the screening, and the logistical and administrative burden of administering the screening program. In general, payers want to see strongly positive outcomes from patients who screened positively to outweigh the cost to screen the population in comparison, and these results need to be seen while members are still enrolled. Part of a solution to bridge the gap between payers and experts is to begin quantifying the value of screenings and building a basis of evidence to support the screening performance and outcomes. Another important factor to gain payer support of screening programs is for the programs to be simple to implement with low costs and low up-front risks.

One of the greatest challenges to genomic data sharing is interoperability, which is the ability of two or more systems or components to exchange information and to use that information. To achieve interoperability, two systems must communicate. Within the broader genomic medicine community, there are multiple sub-communities that have different standards (e.g., Clinical vs. Research) and these standards must be explicitly stated. When there is a gap in communication, one of the most scalable routes to bridge the gap is by having the two systems adopt common standards to meet in the middle. Two groups that are currently working to bridge the divide between the clinical and research communities are HL7 FHIR (Health Level 7 Fast Healthcare Interoperability Resources) and GA4GH GKS (Global Alliance 4 Genomics and Health Genomics Knowledge Standards). These groups are aiming to use aligned standards to take data from clinical reporting and use it seamlessly with research data.

The Mayo Clinic genomic medicine program has learned that data linkages must be maintained robustly to allow for the appropriate use of the data and to ensure the data are FAIR (Findable, Accessible, Interoperable, and Reproducible) to avoid scenarios where data in an EHR are shared from one provider to another using identifiers/indicators that were retired long ago. To maximize the value of population screening data for stakeholders, new systems must be able to manage the data for many years and outlast the clinical systems that host them.

The importance of integrating genetic testing and population screening into EHRs was a frequent theme of the meeting, which the PennChart Genomic Initiative program is tackling by optimizing their EHR to integrate genomic medicine in a very iterative process. The initial steps of this work were taken almost ten years ago when the naming conventions of genetic testing results data were standardized across the institution, and the program has since added a "Precision Medicine" tab within the EHR/PennChart where legacy data of over 17.5K results were migrated. The uptake of genetic test ordering and results has also significantly increased since the start of the program in 2020 and has proven to save time for providers.

The benefits from genetic screening can be hard to identify due to multi-level barriers to communications of providers/patients, billing and access to service, and ongoing development of programs. Another key issue when looking at the benefits of screening is the diminished effect a test has when moved from a highly controlled environment to the uncontrolled environment of the real world ("voltage drop"). Even if a screening were 100% effective, the benefit of the screening still relies on other aspects like system adoptions, changes in medical management, and individuals following stated guidelines. Implementation science will play a key role in breaking these barriers to engage stakeholders from the planning stage all the way to adaptation to understand how to achieve equitable benefits and have continuous evaluation.

In summary, this session addressed the barriers population screening faces, beginning with the gap between payer and expert understanding of the value of screening, the lack of an evidence base to support

screening, and the issues with sharing the genomic medicine data. Progress has been made to tackle some of these barriers, but as a community there needs to be a clear path forward that is scalable and engages stakeholders at all steps to ensure equitable benefits are built into the systems from the ground up.

Session 6: Discussion

Individuals who have a clinical diagnosis of hereditary conditions but have not had a genetic test can be problematic. Ambiguity of the governance of genomic indicators such as *"BRCA2* carrier" or "Li-Fraumeni syndrome" adds complexity since some providers can add/remove the data. This highlights the need for a governance model to ensure information is not removed when it is not meant to be.

A frequent topic from this discussion was the need to make patient data portable from one health care system to another and standardized to ensure it is readable and compelling from the payer perspective too. Engagement and patient perspectives should also be key factors in the design process. A space that could use more computational support is building a workflow in the EHR for physicians to do diagnostic thinking where results/conclusions of tests can all be in the same space.

Getting buy-ins from health care systems, payers, and users begins with disseminating current findings and lessons learned. Genetic screening in particular gets extra scrutiny from payers as there might be a misconception that "genomic" equates to "rare." An idea to consider is a system where reimbursement is dependent on the integration of data into an EHR to ensure the value of the data does not diminish. There will not be one right answer on how to implement screenings—individuals and institutes should accept responsibility to educate others on the current standards being used, avoid collaborations with groups who do not align with the current standards, and avoid labs that do not share data broadly.

Session 7: Research Directions

Pre-testing phase

The most important takeaway for research directions in the pre-testing phase is engagement. Implementation science should be used to think about engagement across a number of different stakeholder types, including patients, clinicians, health systems, payers, and the public health realm. The Researcher Engagement Framework from All of Us is a good example of this. It covers various levels of engagement from individual to societal. Additionally, the National Academies of Medicine has worked on what is called a "dynamic relationship," which focuses on *meaningful* community engagement.

Additionally, there needs to be a standardized approach to inform inclusion or exclusion of genes or variants for population screening. Research needs to be done on what the next form of evidence-based medicine looks like—that is, "Evidence-based medicine 2.0." Research also needs to be done on the standardization of outcomes and cost, including defining cost outcomes (e.g., QALYs, PMPM).

One way to facilitate comprehensive and equitable implementation of population screening is to use an evidence-based framework to conduct pre-implementation. Equity across multiple dimensions and from the perspectives of different populations and communities should be considered. Pilot studies for population screening for near-Tier 1 conditions are needed to provide the "last mile" of evidence. The genomics community should engage with the prevention research community to co-develop genomic prevention research projects. Population genomic screening in the public health setting will have different rules, regulations, and policies from the research setting; these differences need to be explored within the context of implementation research, and a learning, sharing network to facilitate shared knowledge is needed to answer the question of how to move from successful projects to widespread implementation.

Testing phase

There are several types of tests: those with a single, specific purpose; opportunistic use of content from one test for a distinct purpose; and broad tests intended for reanalysis. Uptake of these tests relates to the complexity of the test and the consent process. Research should be done on reducing the complexity of and standardizing pre-test consent and ordering, determining when GCs are needed and whether they can be disconnected from the clinic, and how to efficiently transmit phenotype and indications for testing.

Today, VUS variants are often returned with P/LP variants if the patient is symptomatic. If asymptomatic screening, typically VUS are not returned, but perhaps they should be indicated on a screening report to reduce surprise if a VUS is later reclassified to an LP/P variant. Carrier screening is an area where further research is needed. Approaches for couple-based screening also need to be developed.

Ultimately, there needs to be research on how to make test results useful and understandable. Research is needed on the value of EHR integration for improving utility of genetic testing; finding a model that fills the need of patient-specific, explicit care recommendations; understanding what labs can provide (e.g., a model to pair a report with physician consultation); and CDS tools.

A genomic learning healthcare system can be one such model, but research is needed to understand how it can be supported. Research is also needed in patient consent for genetic testing to ensure the most robust learning from the data, and to understand what type of infrastructure is needed to most effectively support reanalysis and reuse of existing data. Additionally, universal quality metrics are needed since secondary analysis might happen in a different laboratory than the one it was generated in. Research is needed on what results can be used directly from the genome and what requires professional interpretation.

Follow-up to testing

Research needs to be done on how to set realistic expectations and how to mitigate the risk of false reassurance. There is value to research into mechanisms that make sure that there's an alignment between what is expected and what is returned.

With generation of data also comes generation of data on penetrance, as well as defining what penetrance means. Additionally, longitudinal follow-up of at-risk persons would be useful, and there is a need for standardization of outcome measures, but following outcomes of population screening will be very challenging. There is a need for research on point-of-care decision support and understanding the role of genetic counseling, integration into the EHR, and AI systems.

There were several suggestions for the *All of Us* program, including modeling population screening and finding ways to increase uptake of cascade testing. Questions and considerations include what accounts for families with higher or lower acceptance and how to facilitate communication of information through the family, as well as effects on family relationships.

Summary and next steps

The Executive Summary details the lessons learned and recommendations from this meeting. All of the presentations and video recordings can be accessed on the GM XV website. In addition to this Meeting Summary, the co-chairs Gail Jarvik and Teri Manolio will consider developing a white paper for publication based on the outcomes of this meeting.