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Genomic Medicine XV: Genomics and Population Screening
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Executive Summary

Welcome, Introductions, and Goals

The Genomic Medicine Working Group (GMWG) convened leaders in genomic medicine and related fields 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.

In addition to items on the agenda, the meeting covered the role of geneticists and genetic counselors in population screening, the potential role of telehealth and AI, the problem of false positives, and research needed for the healthcare system to be ready to handle population screening.

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

This session assessed current readiness for widespread population genomic screening and key differences between population genomic screening and current genomic and genetic practice. Highlights include:

- Genomic testing is not exceptional—it performs like any other test. As with any test, performance depends on context, particularly on the prior probability of the condition. Patients referred for clinical testing have a higher prior risk of disease compared to the general population.
- Genomic screening for disease risk is challenging due to an increased rate of false positives when compared to genomic testing for an indication; it also prompts a pivot of traditional genetics from diagnosis and treatment to prevention.
- Medical actionability is not sufficient to justify population screening; clinical utility is needed.
- Current clinical screening strategies miss significant numbers who have high-risk variants.
- The type of clinical intervention indicated by positive screening (e.g., diet change vs. surgery) influences the tolerance for false-positive screening results; patient preference also varies.

Recommendations included:

- Effective access to interventions that improve outcomes should be the primary driver of selecting screening conditions, which should be identified with engaged populations and experts.
- A timeline for implementation of population genomics in the U.S. should be created.
- Probabilistic models for conditions to be screened similar to the Richards criteria for variant classification should be developed, explicitly laying out the information needed for selection.

Session 2: Genomic Screening Technologies

This session looked at the current state of clinical methods for population genomic screening, as well as lessons learned from screening programs such as newborn screening (NBS). Highlights include:

- Stress testing clinical testing pipelines is critical before implementing high-throughput screening.
- When testing, result parameters need to be clearly communicated to providers and participants, and re-contact and re-analysis expectations must be defined in advance.
- There is inequity in variant interpretation due to a lack of data from underrepresented groups.
- Potential harms of reporting and treating false positives should be recognized and "disutility" or "number to harm" should be carefully considered.

Recommendations included:

- Screening tests are needed that distinguish early- from late-onset forms of disease.
- Interpretation of compound heterozygosity for recessive diseases is an important research aim.
- Clinical hand-off and follow-up of positive tests to clinical providers needs to be established for adult screening, along with pathways for diagnostic testing and pre-symptomatic interventions.
- Improved population-based estimates of prevalence, natural history, and penetrance of monogenic conditions are needed and may potentially be derived from large biobanks.
- Appropriate genetic counseling approaches should be defined for persons with negative tests.
- Potential harms of false reassurance from negative tests should be studied and minimized.
- More research is needed on biology of penetrance and evidence needed to prove pathogenicity; MaveDB, IGVF, and related programs should be engaged and connected with clinical research efforts such as ClinGen and GREGoR to address clinically relevant variants.

Session 3: Logistics of population screening

This session covered who should return genetics results, strategies for population screening, and the importance of inclusion of diverse genetic ancestries in databases. Highlights and solutions include:

- Primary care is the ideal place for genomic screening given the broad prevention orientation of primary care providers (PCPs), but specialists seem more enthusiastic about implementation.
- Lowering the burden of disease involves implementing strategies targeting both high-risk individuals and the general population.
- Increasing equity and diversity in genomic research and in datasets is essential to implementing equitable and robust genomic screening.

Recommendations included:

- Sample tracking is a mundane but critical logistical issue in screening that needs consideration.
- Implementation research is needed to compare genomic screening in primary vs. specialty care.
- Genomic and primary care leaders should meet to share their perspectives on emerging evidence and understand what is needed to increase uptake of genomics in the primary care space.
- Genomic screening should be implemented gradually rather than all at once.
- Decision support systems, referral patterns, and workforce education are needed for PCPs as are models for integrating genomic screening and preventive interventions in primary care.

Session 4: Community engagement and population genomic screening

This session examined the role of *meaningful* community engagement. Highlights and solutions include:

- Even with the expanded ACMG secondary findings panel, only five medically actionable genes have variant information specific to Indigenous peoples and not all labs may test for them.

- The researcher community needs to be proactive with engagement, and work to overcome mistrust and improve equity rather than simply recruit underrepresented populations.
- True engagement requires dedication to co-creation and partnership from inception of the study.
- Tribal nations, due to their sovereignty, can act in ways other underrepresented populations can't necessarily—this should be taken into consideration when doing research.

Recommendations included:

- Population screening should be piloted starting with the Tier 1 list, then expanded to add tests that are almost ready and identifying the gaps to be filled to make them incontrovertible.
- Engagement needs to be proactive, seeking out community values and aspirations, respecting sovereignty and self-determination, and acknowledging previous harms and power imbalances.
- Selection and interpretation of screening tests should be informed by non-genetic factors including social determinants of health that affect diverse communities.
- Advances are needed in evidence-based methods that appear not to have evolved in > 12 years.
- Patients should be directly engaged in developing educational materials and results reports.
- Research is needed on improving the care pathway for those in low-access areas.

Session 5: Evidence Needed to Support Screening

This session examined the value proposition of genomic screening—involving both cost and improved health outcomes. Cost, patient motivation, and equity were discussed. Highlights include:

- Value-based care considers improvements in patients' health outcomes as well as cost.
- Standardizing outcomes is critical to compare research effectively.
- Screening for all three Tier 1 conditions is cost-effective if screening starts before age 40. Conditions need to be combined for screening as most are not cost-effective on their own.
- False reassurance from negative tests and subsequent neglect of preventive measures can eliminate cost-effectiveness of screening; research is needed on responses to negative tests.
- Patients are more engaged and less cautious than clinicians believe; paternalism is problematic.
- While sequencing technology might improve, reanalysis of available sequences can be effective.
- Still unresolved is where genomic data will be housed and whether/how it will follow the patient.

Recommendations included:

- Identifying health outcomes important to patients is crucial for successful uptake of screening.
- Systems are needed for enabling genomic data to follow patients throughout their lifespan.
- Research is needed on cost-effectiveness of polygenic risk scores and genomics-informed risk.

Session 6: Obstacles to Screening

This session provided an overview of current obstacles to gaining support from payers for screening due to the lack of an evidence base and the challenges of sharing the data across systems. Highlights include:

- If clinical benefit can be demonstrated, cost is less of an issue to payers.
- Disconnecting screening from healthcare, such as making expanded results from sequencing at birth available for review at age 18 when voting or getting driver's license, may improve uptake.
- Simple, low-cost screening modalities with low up-front risks may improve payer support.
- Implementation science can help achieve equitable evaluation and benefits to all and provide continuous engagement with a wide variety of stakeholders.

Recommendations included:

- Minimal standards should be imparted to clinicians of when to test and how to return results.
- Research is needed on when consent is and is not needed for clinical genomic testing/screening.
- Data and terminology standards need to be harmonized across research and clinical settings.
- Research is needed on knowledge management, including types of derived data, tracking data provenance, and keeping data available in both computer and human readable (PDF) format.
- Research is needed on whether and how requiring use of standards and incorporation in EHRs generates more value or improves outcomes.

Session 7: Research Directions

This session identified research directions before, during, and after genomic testing. Notably, both here and above, many recommendations are relevant to genomic medicine and genetic testing in multiple contexts and not only in population screening, Recommended research directions include:

- Development of a probabilistic model for adding genes for screening, similar to Richards criteria
- Development or improvement of evidence-based models for evaluating genomic screening tests
- Improved estimates of numbers needed to screen, penetrance, natural history of conditions
- Approaches to ensure equitable implementation of population screening and follow-up
- Pilot studies for near-Tier 1 conditions, including engagement of prevention research community and examination of policies for population genomic screening in the public health setting
- Development of care networks to facilitate shared knowledge and transportability of results
- Improved understanding of biology of penetrance, impact of compound heterozygotes, metrics of cost, and potential differences between peripheral blood samples and germline findings
- Approaches to engaging communities to be screened in all aspects of study design and execution
- Methods to reduce complexity of, and standardize, pre-test consent and ordering
- Understanding how single- vs. multi-use tests differ in sensitivity, cost, and best settings for use
- Improved methods for transmitting phenotype data and indications for testing to laboratories
- Examination of when genetic counselors/assistants are and aren't needed and whether they can be disconnected from clinical settings
- Improved design of genetic reports to highlight what is important and set aside what is not
- Approaches to support preconception "couple-based" carrier screening rather than mother-first
- Methods enabling labs to link genetic results reports with physician consultation and CDS tools
- Approaches to consent that accommodate patient preferences yet maximize knowledge generation
- Methods to support reanalysis and reuse of existing data, including secondary analysis/use by different lab and identifying results that can be used directly without professional interpretation
- Examination of "how long" sequencing data can be re-used before they should be generated anew
- Methods to support ongoing contact/communication with patients as genomic knowledge changes
- Methods to enable long-term follow-up of screened individuals to assess impact, outcomes
- Approaches for setting realistic expectations for genomic screening, mitigating risks of false reassurance, and facilitating accurate communication of results within families
- Potential for using *All of Us* data to model impact of population-wide genomic screening
- Potential roles for artificial intelligence in reporting and following up screening results
- Methods for storage, access, and transportability of screening data within health system, research enterprise, separate "data bank," and/or with screened individuals

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Additional information can be found on the GM XV website: www.genome.gov/event-calendar/genomic-medicine-xv-genomics-and-population-screening