Session 1: Laying the Groundwork

- Basic principles of testing for disease and risk: importance of disease prevalence in predictive value of test
- Goal of genetic testing/reporting will shift from consoling and adapting to motivating health behaviors to reduce genetically-informed risk
- Screening strategies addressing Tier 1 conditions (9 genes) probably consensus starting point– what conditions should be added
- Clinical utility has to be *sine qua non,* returning genetic findings should prompt intervention that results in improved health; medical actionability insufficient
- Engaged population and engaged expertise should drive screening list– *APOL1* and *TTR* important in some populations but not others
- Need timeline and milestones
- Need "Richards criteria" for selecting screening tests and populations
- Need research on when we do and don't need genetic counseling
- How to incorporate individual patient preferences– AI and online tools
- Study biology of penetrance, evidence needed to prove pathogenicity

Session 2: Genomic Screening Technologies

- Lessons learned in optimizing high-throughput screening
- Set high bar for adopting technologic advances for screening; quality metrics
- Need research on assessing compound hets especially when second is VUS
- Distinguish early- from late-onset forms, pre-symptomatic management
- Inequity in variant interpretation– lack of data from underrepresented groups
- Need to figure out hand-off of positive tests to clinical providers
  - f/u for children funded by HRSA and still less than half get f/u
- Need better estimates of prevalence of monogenic diseases, natural hx, age-related prevalence – biobanks can help
- Recognize potential harms of false +, consider “disutility”
- Define appropriate role for GC with negative testing, understand how pts respond to negative tests
  - Pt with very clear phenotype (frequent polyps, long QT) and negative genetic testing still needs follow-up but with no phenotype don’t need GC
- Engage MaveDB, IGVF, high throughput assays to identify screening targets

Session 3: Logistics of Population Screening

- Appropriate locus for managing results is primary care– currently already doing lots of preventive screening, but specialists seem more engaged with genetics
- Barriers to specialty care greater than primary care, could increase disparities
- PCPs should not become GCs– study multiple models of CDS for what they need to handle consent, results, referring focused on one screening
- Consider meeting of genomic and PCP leaders to share perspectives and relative weights they place on emerging evidence; address PCP skepticism
- Guidelines need to be simple
- Need meaningful engagement from outset; disparities start *in utero*
- Integration with clinical care can improve access to screening and follow up
- Identify, anticipate past harms and avoid building them into future systems
- Research gaps– incorporate SDOH and ancestry; identify and limit barriers to participation; incorporate principles of equity
    - Broaden ancestries in research databases, improve descriptions of ancestry
    - Research in clinical decision support (CDS)

Session 4: Community Engagement and Genomic Screening

- Need to be proactive, seek out community values and aspirations, respect sovereignty and self-determination, acknowledge harms, power imbalances
- Not engagement, recruitment, selling benefits; it's overcoming mistrust, thinking proximally about health, data decision equity, equity metrics
- Only 5 ACMG variants relevant to AI/AN, especially CRC genes
  - When refer pt out what kind of test are they getting– variants for AI/AN?
- Tribal nations can set rules that other URM groups can't; marginalized communities don't have organized structures for consultation
- Policies and governing agencies for research and public health very different
- Need advances over EBM methods that have remained fixed for > 12 years
- What evidence needed to get to more conditions– identify tests almost ready for prime time and gaps to fill to make them "bullet proof"
  - Fund appropriate healthcare systems to pilot those almost-ready
- Engage pts in development of educational materials, results reports
- Engagement not enough, true co-creation from beginning of project

Session 5: Evidence Needed to Support Screening

- Value– measured improvement in outcomes for cost of that improvement
- Critical to identify health outcomes of importance to pts
- Trivial cost of confirmatory testing after targeted sequencing; 1-2% of screened
- Screening all 3 Tier 1 cost-effective up to age 40 ($100K/QALY)' ?HCM
- False reassurance of negative tests (10% of 30yo) eliminates cost-effectiveness
- Have to combine conditions to get good value
- Leadership engagement strong predictor of clinician satisfaction
- Perils of paternalism– not as grim as clinicians predict; who mistrusts whom
- Still struggling with how sequence data follow pt across systems through life
- If there's clinical benefit cost is less of issue, reducing harms is biggest concern; screening at younger ages might be looking too early for intervention timing, increased anxiety
- Consider making sequencing results available for review at age 18 when voting or getting drivers license– disconnect from healthcare
- Post-testing interventions for high-risk people– research to find right follow-up models, help pts/provider understand recommendations and increase uptake

Session 6: Obstacles to Screening

- Payers care more about health outcomes than cost savings
- Payers asked to take upfront costs of screening with little control or investment in long-term outcomes; benefit in 1.7-2.5 yrs
- Payers (and everyone else) will prefer simple, low cost, low risk screening
- USPSTF weighed heavily, if not grade A or B evidence will be tough
- Research opportunities: data and terminology standards, define types of derived data, knowledge management; transportability by pt
- Roadmap to genomics-enabled EHR in PennChart Genomics Initiative (dissem)
- Great list of challenges, anticipated (start small with very specific use cases) and unanticipated (much higher demand for dissemination)
- Incorporate equity into ImpSci: Reach (all equitably), Effectiveness (negative effects), Adoption (low resource settings), Implementation (who didn't implement and why), Maintenance (equitably maintained)

Session 7: Research Directions

- EBM 2.0– who's developing that?
- How to incorporate other types of data– qualitative, mechanistic
- Cost metrics for different stakeholders (QALY, PMPM)
- Pilot studies for near Tier 1 conditions
- Engage with prevention research communities for designing research
- Unique aspects genomics screening– blood vs. germline

- Tests with single purpose vs. multi-use, opportunistic use
- Uptake discouraged by complexity and responsibility for management
- Equitable interpretation/return of single lab submissions in ClinVar
- Research on returning VUS and sub-tiering VUS-lows, etc.
- Carrier screening– report VUS if partner has P/LP, make couple based, move to preconception
- How can labs provide specific guidance on specific pt– pair lab reports with physician consultation, CDS; patient choices

Session 7: Research Directions

- How to consent pts to ensure most robust learning, case-level data sharing
- How to provide f/u data from clinician or pt back to lab to improve interpret'n; importance of bidirectional communication
- How to recontact for re-analysis– through portal, CSER's GenomeDiver
- Research to design best report format across labs, could conceivably get all groups together to agree, depends on other systems they integrate with
- Better aligning GA4GH standards

- Generate data on penetrance, learn from longitudinal f/u
- Model impact of screening in AoU RP
- How to facilitate communication within families
- Should AoU RP encourage enrollment of family members
- Different models for providing sequence data to ppts– DNA databanks
- Concept of false reassurance
- Compare our self-flagellation to others

GMXV: Genomics and Population Screening

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