Communicating Results in GxE Research: Lessons from Genomics Return of Results Policies and Practice

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Statement Honoring the Land on which the University of Washington Stands

We acknowledge the land we occupy today as the traditional home of the Tulalip, Muckleshoot, Duwamish and Suquamish tribal nations. Without them we would not have access to this working, teaching and learning environment. We humbly take the opportunity to thank the original caretakers of this land who are still here.

https://www.realrentduwamish.org

OVERVIEW

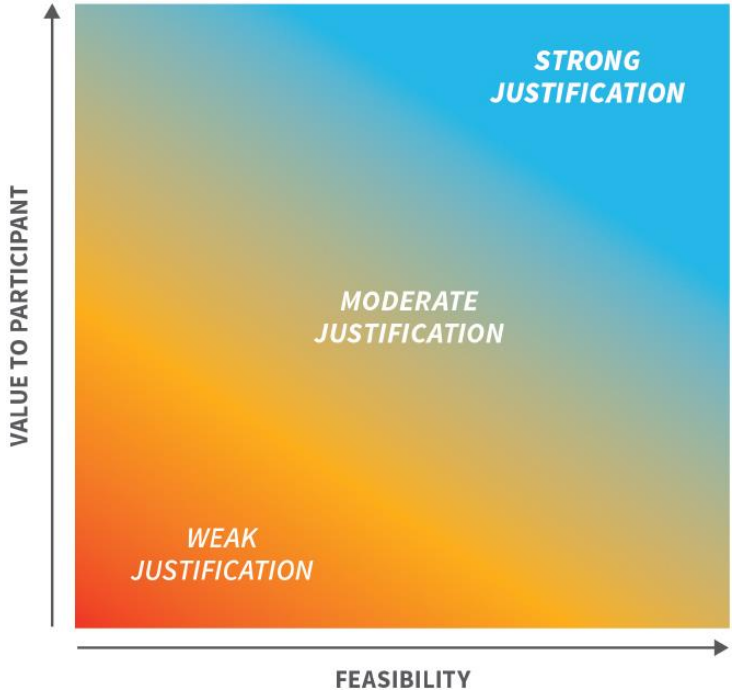
- Offering individual research results to genetic research participants
- Disclosure of actionable genetic research results
- Disclosure of other types of research results
  - Multifactorial (often complex) risk
  - Non-actionable: Genotype-Driven Recruitment
  - Non-actionable: Stakeholder Views

RESULT RETURN RECOMMENDATIONS HAVE SHIFTED OVER TIME

- Return of individual research results discouraged for many years
- As genetic research advanced, it was recognized that actionable, analytically and clinically valid, results would often be generated
  - *Beneficence* supports offer of such results to participants
- Ongoing debate about "duty to look" for actionable results

NASEM's 2018 RECOMMENDATIONS Returning Individual Research Results

- Support decision making regarding the return of results on study-by-study basis
- Promote high-quality individual research results
- Foster participant understanding of individual research results
- Revise and harmonize current regulations



PLANNING IS TRICKY ENOUGH… (one possible framework)

STUDY PURPOSE	PLACE OF RoR IN STUDY DESIGN	NATURE OF RESULT	DECISION	TIMING	CONSENT INFORMATION
Test specific hypothesis	Study objective (return of results planned as part of research objectives)	Clinically actionable, valid and urgent	Return result	2-7 days	Specific objective and plans for return
		Clinically actionable, valid and non-urgent	Return if feasible	Scheduled	
		Nonactionable, valid and non-urgent	Discretion	Scheduled	
		Nonactionable, uncertain and non-urgent	Discretion	Scheduled	
	Only if indicated (no return of results planned as part of research objectives)	Clinically actionable, valid and urgent	Return result	2-7 days	Specific objective, likelihood of findings to return, plan for return
		Clinically actionable, valid and non-urgent	Return if feasible	Scheduled	
		Nonactionable, valid and non-urgent	No return	N/A	
		Nonactionable, uncertain, and non-urgent	No return	N/A	
Open ended (Prospective or hypothesis free)	Study objective (return of results planned as part of research objectives)	Clinically actionable, valid and urgent	Return result	2-7 days	General objective, currently foreseeable results and plan for return
		Clinically actionable, valid and non-urgent	Return if feasible	Scheduled	
		Nonactionable, valid and non-urgent	Discretion	Scheduled	
		Nonactionable, uncertain and non-urgent	Discretion	Scheduled	
	Only if indicated (no return of results planned as part of research objectives)	Clinically actionable, valid and urgent	Return result	2-7 days	General objective, likelihood of findings to return, plan for return
		Clinically actionable, valid and non-urgent	Return if feasible	Scheduled	
		Nonactionable, valid and non-urgent	No return	N/A	
		Nonactionable, uncertain and non-urgent	No return	N/A	

Fullerton et al., unpublished

DISCLOSURE OF EVEN IMPORTANT, INDIVIDUALLY-RELEVANT, RESULTS IS COMPLEX

- **Type of Result**
  - Diagnostic
  - Secondary (Incidental)
- **Who Communicates**
  - Genetic Counselor
  - Other Staff or Doctor
- **How Returned**
  - In Person
  - Via Letter or Website

Challenge (Genomic Result Return)	Method to Address Challenge
Multiple results	Re-iteration and restating results. Open ended questions to assess understanding. Multiple sessions. Follow up communication.
Unmet expectations	Explore and set realistic expectations in the consent session. Acknowledgment and validation of feelings of disappointment and frustration.
Uncertainty	Review of current limitations in genomic knowledge. Reassurance that communication pathways are open and updates may be available.
Unanticipated Results	Facilitate feelings of empowerment to have this knowledge. Ability to seek early screening and prevention or plan for the future
Communication of results with family members	Encourage reflection of this in the consenting session. Make a plan in the disclosure session.
Overwhelmed or not engaged	Anticipate, acknowledge, foster a relationship of ongoing communication and options for follow up conversations.
Provider's expectations	Recognize one's own biases and misconceptions. Reassess one's own at regular intervals.

Wynn et al. (2018) *BMC Med Genomics*

Factors Influencing Participant Understanding	Participant Emotional Response	Disease Burden	Logistical Challenges
• Low health literacy	• Anxiety related to uncertain results	• Overwhelmed by health issues	• Using a medical interpreter
• Language discordance between participant and provider	• Parental distress	• Competing medical priorities	• Mode of delivery
• High-level genetics concepts	• Disappointment due to unmet expectations	• Parental condition	• Distance to the academic medical center
• Complex results	• Overwhelmed by unexpected results		• Lack of personal transportation
• Ambiguous results			• Long work hours
• Distrust in the medical system			• Coordinating family testing

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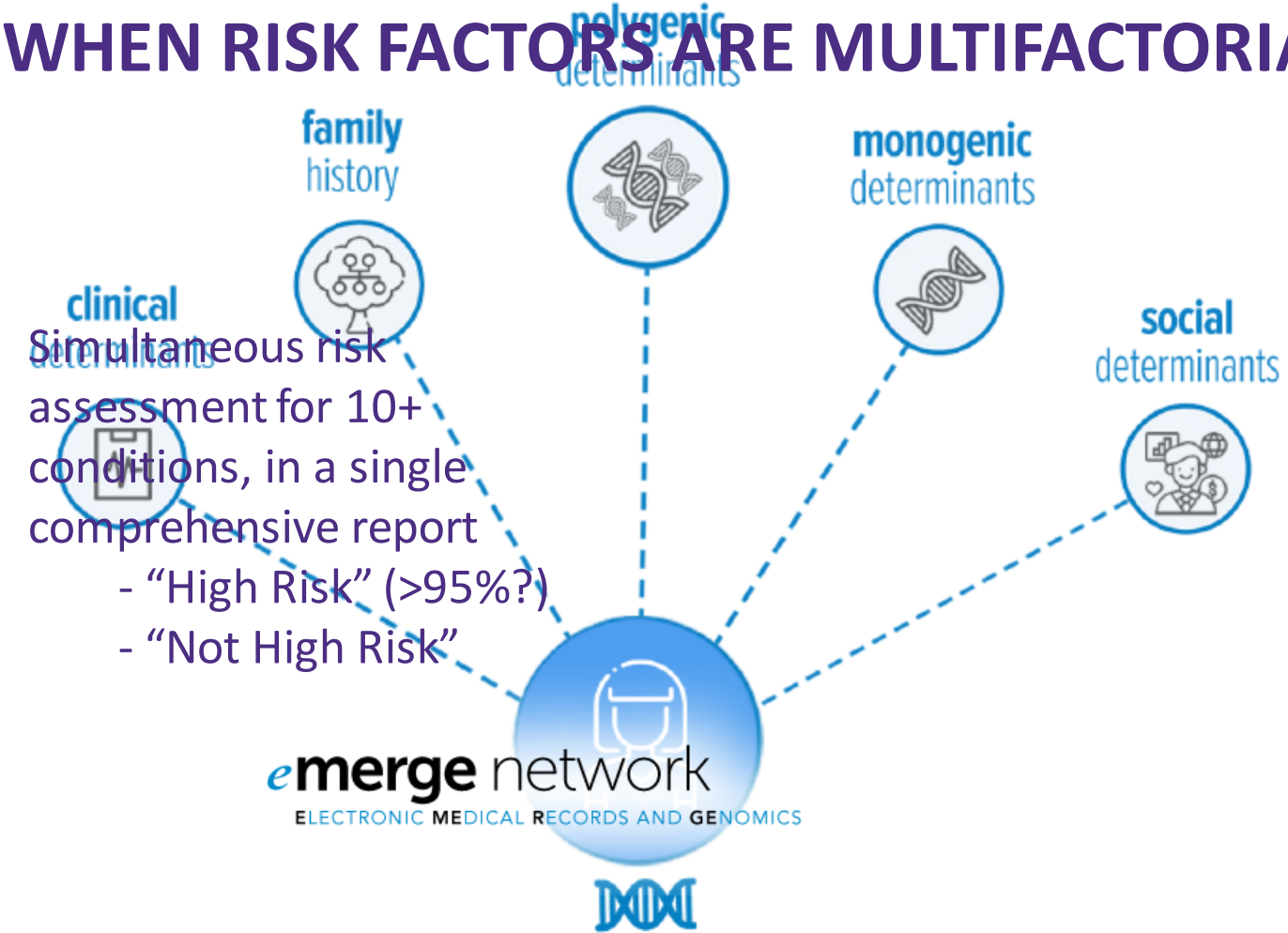
Clinical Sequencing Evidence-Generating Research

Suckiel et al. (2021) *J Personal Med*

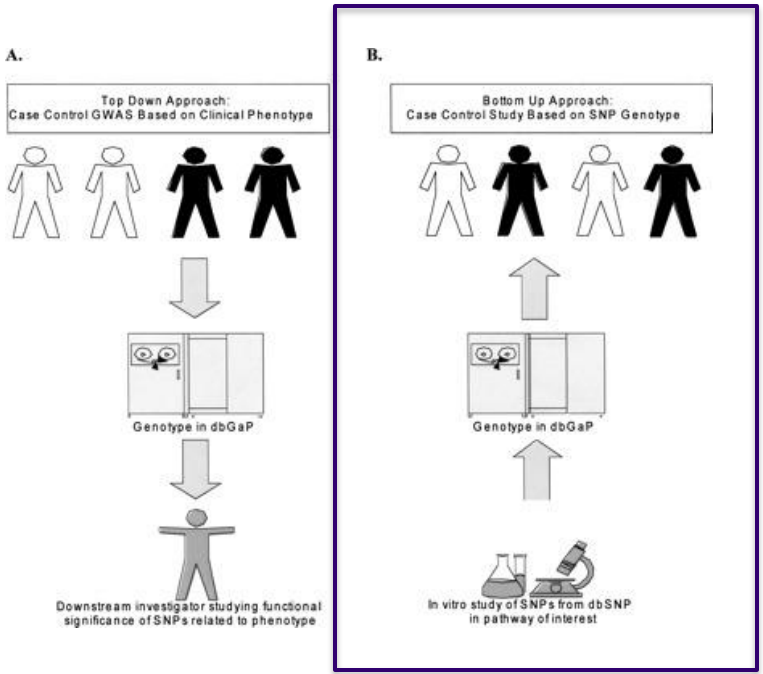
WHEN RISK FACTORS ARE MULTIFACTORIAL?



Simultaneous risk assessment for 10+ conditions, in a single comprehensive report

- “High Risk” (>95%?)
- “Not High Risk”

COMMUNICATION WHEN 'WORK IN PROGRESS' as Most GxE Research Will Likely Be?



"Genotype-Driven Recruitment" McGuire & McGuire (2008) *Genom Res*

SUCH COMMUNICATION REQUIRES GREAT CARE
Beskow et al. (2012) *Hum Genet*

- **Normal clinical validity and/or utility standard for return will rarely be met**
- **Participants should be offered results as they are recruited to additional research**
  - "A careful series of steps should be used both to avoid leaving prospective participants uninformed about the purpose of the study and to maximize their right not to know unwanted genetic information"

AND BALANCING COMPETING CONSIDERATIONS

Non-maleficence

Respect

SOLICITING STAKEHOLDER PERSPECTIVES

e.g. Return of Nonactionable *APOL1* Research Results

- **Rationale supporting return: benefit**
  - **Personal value, expectations of actionability**
  - **Demonstration of respect for ppts, broader community**
- **Caveats noted (most fr professional stakeholders)**
  - **Psychological burden**
  - **Potential for misunderstanding**
  - **Stigma and discrimination**
  - **Research trade-offs**

West et al. (2022) *JERHRE*

SUMMARY

- **Where feasible, individual research results should be offered to genetic research participants**
- **Disclosure of – even actionable – genetic research results can be challenging**
- **Disclosure of multifactorial or non-actionable genetic results, which can be expected in much GxE research, poses greater challenges**

WITH GRATITUDE TO

- UW Human Subjects Division (esp Karen Moe, Maria Savage)
- Clinical Sequencing Evidence-Generating Research (CSER) Consortium (U24 HG007307 Jarvik et al)
- Electronic Medical Records & Genomics (eMERGE) Network (U01 HG008657 Jarvik/Crosslin)
- Ethical Approaches to Genotype-Driven Research Recruitment (RC1 HG005787 Beskow)
- Community-Based Evaluation of *APOL1* Genetic Testing in African Americans (R01 HG007879 Burke/Young)