Designing for Accelerated Translation (DART) of emerging innovations in health

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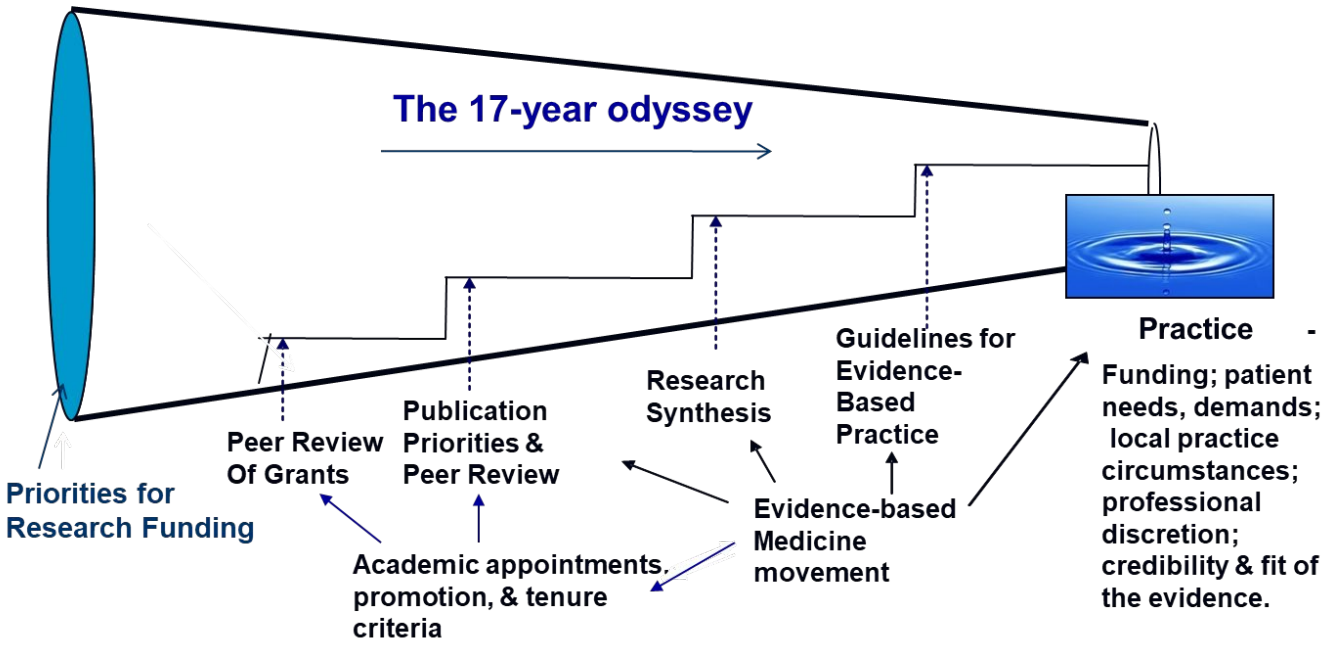
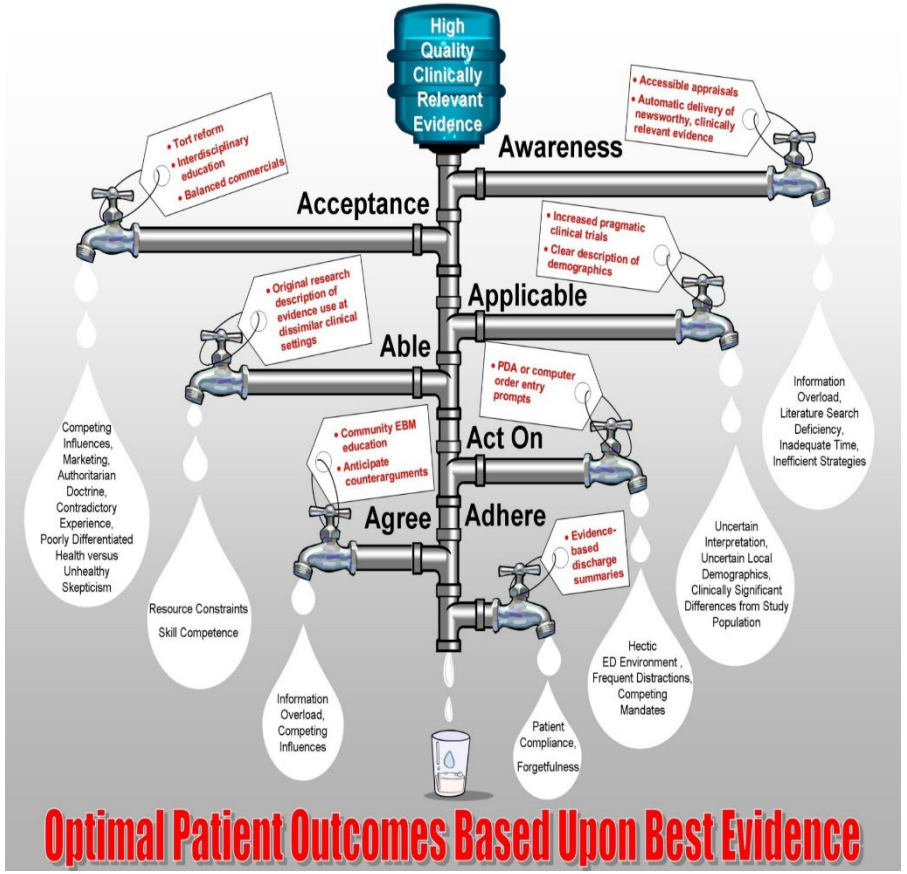
17 years for 14% of research discoveries to be integrated into practice



Balas & Boren. in van Bemmel & McCray, Yearbook of Medical Informatics. 2000



Pathman et al. Med Care. 1996.

Things may get worse

- Healthcare is increasingly multilevel
  - Barriers at the patient, provider, health care system, and policy levels
- Healthcare is increasingly burdened
  - Pragmatic research on chopping block if not aligned with real-world problems and routine workflows

Things may get better

- Rapid Cycle Research – momentum toward timely, contextually-informed innovation (recent NCI workshop, etc)
- Rapid iterative processes to address pragmatic problems, resulting in "better care faster" (Johnson et al., 2015)
- "…implementation cannot be left as a post hoc procedure." (Mohr, Riper, Schueller. JAMA Psychiatry 2018)

“What is the minimum level of evidence needed for implementation?”

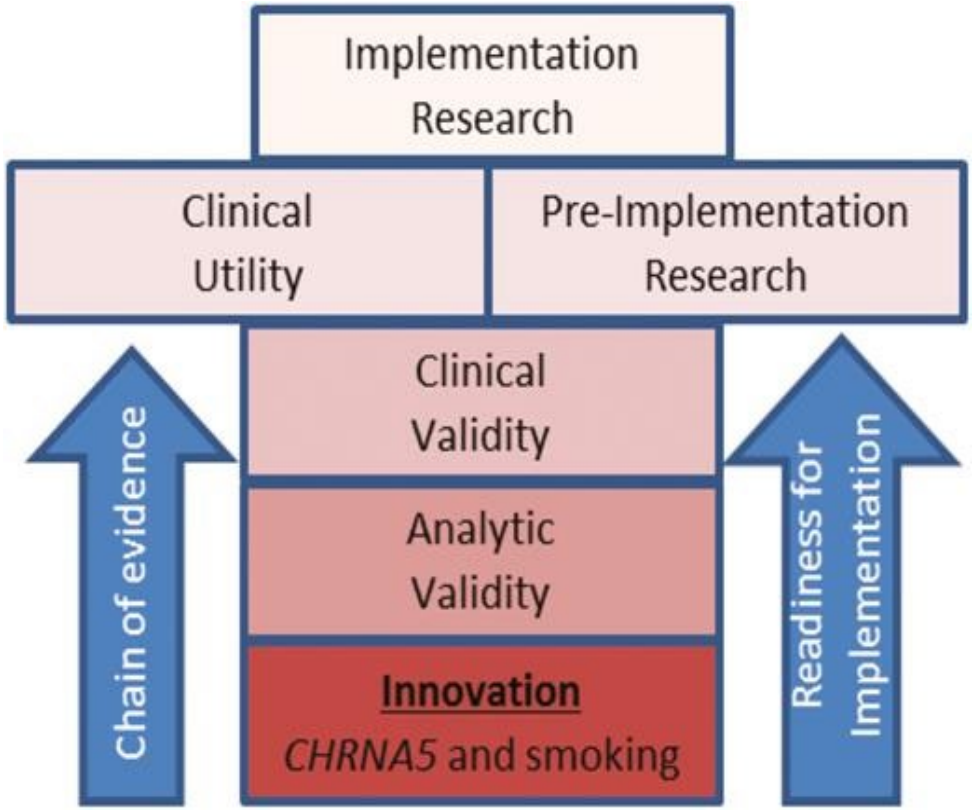
“When can we begin acting on the evidence, even as it rapidly evolves?”

“These are the questions we’re asking in our mHealth and genomics work!”

“How can implementation science inform this work at an earlier stage?”

“Lots to unpack here – let’s write a paper”

Merging implementation science with biomarker research



- When is a genomic biomarker ready for implementation?

  → Examine the chain of evidence (CDC, 2009)

  Analytic validity – Reliability of biomarker test
  Clinical validity – Strength of association
  Clinical utility – improve care, health behavior, perceived benefit

- Typical Approach: Demonstrate utility, then consider implementation issues

- Proposed Approach: Assess implementation context *alongside* clinical utility

Ramsey, A. T., Chen, L. S., Hartz, S. M., Saccone, N. L., Fisher, S. L., Proctor, E. K., & Bierut, L. J. (2018). Toward the implementation of genomic applications for smoking cessation and smoking-related diseases. *Translational behavioral medicine, 8*(1), 7-17.

What's behind the idea of DART?

Key Premise #1	**Translation of evidence to practice is unnecessarily slow.**
Hot-Take #1	D&I research should not be viewed merely as a final step in the translational process.
Hot-Take #2	Without radically different approaches to accelerating translation, diffusion of evidence to practice will remain slow.
Key Premise #2	**Translation of evidence to practice is a dynamic process.**
Hot-Take #3	Researchers are responsible for considering implementation needs "early and often".
Hot-Take #4	All health research should aim to address an actual problem or need.
Hot-Take #5	Much evidence can be acted upon even when uncertainty of effectiveness is moderately high, recognizing that this evidence is evolving and subject to frequent reevaluation.

Is evidence of effectiveness all that matters?
What else informs an innovation's readiness for implementation?

Pace of implementation **(P)** is a function of:

- strength of **evidence** **(E)** – effectiveness, utility

- **demand** **(D)** – urgency, existing alternatives, stakeholder pull
- **risk** **(R)** – potential clinical harms, risk from ***not acting*** on available evidence
- **cost** **(C)** – financial expense, resource intensiveness, disruptive effects

$$P = f\left[\frac{(E * D)}{(R + C)}\right]$$

Journal of Clinical and Translational Science

Implementation, Policy and Community Engagement Special Communication

Designing for Accelerated Translation (DART) of emerging innovations in health

Alex T. Ramsey[1,*], Enola K. Proctor[2], David A. Chambers[3], Jane M. Garbutt[4,5], Sara Malone[2,4], William G. Powderly[5] and Laura J. Bierut[1]

Guide to assessing and accelerating implementation readiness

Evidence	Demand	Risk	Cost

Ramsey, A. T., Proctor, E. K., Chambers, D. A., Garbutt, J. M., Malone, S., Powderly, W. G., & Bierut, L. J. (2019). Designing for Accelerated Translation (DART) of emerging innovations in health. *Journal of Clinical and Translational Science, 3*(2-3), 53-58.

Application to a precision medicine innovation: Genetics of smoking (*CHRNA5* variants)

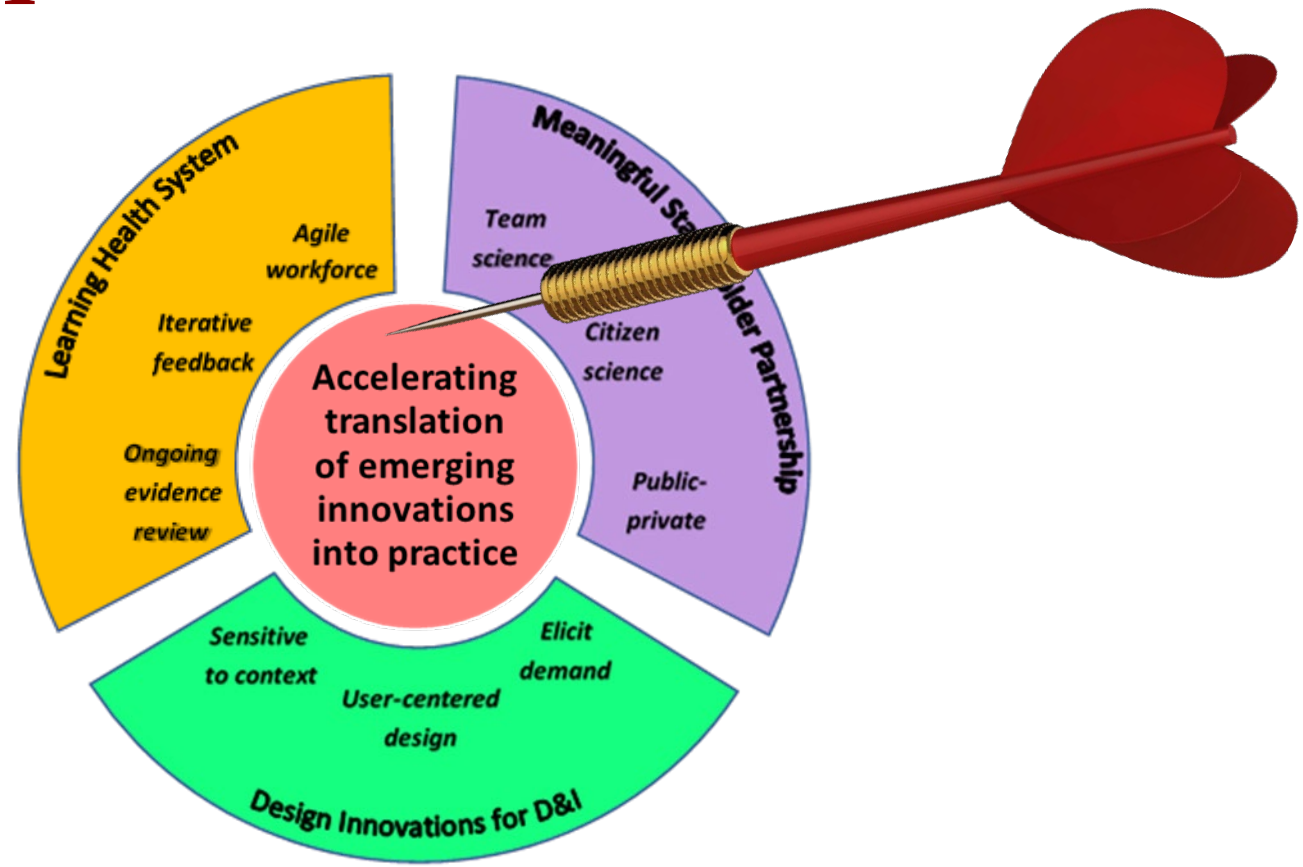
Evidence	Demand	Risk	Cost
Moderate	High	Low	Decreasing
Strong Analytic and Clinical Validity Clinical Utility needed	> 2 million people genotyped for direct-to-consumer genetic testing > 90% current smokers wanted genetic results to guide smoking cessation	After receiving genetic results: Never smokers do not start smoking Former smokers do not relapse No increase in anxiety or depression No decision regret	Genome array is < $200 Sequencing is < $1000 Single test with durable and broadly-applicable results
Hancock et al 2018 *Curr Psychiatry Rep* Ramsey et al 2018 *Transl Beh Med*	Yamamoto et al 2017 J Hum Genet Ramsey et al 2020 *Cancer Prev Res*	Lipkus et al 2015 *Nicotine Tob Res* Hartz et al 2015 *Genet Med* Olfson et al 2016 *Nicotine Tob Res*	EMR and Genomics (eMERGE) Network Implementing Genomics in Practice (IGNITE) Network

Ramsey, A. T., Proctor, E. K., Chambers, D. A., Garbutt, J. M., Malone, S., Powderly, W. G., & Bierut, L. J. (2019). Designing for Accelerated Translation (DART) of emerging innovations in health. *Journal of Clinical and Translational Science, 3*(2-3), 53-58.

Accelerating (or optimizing the pace, if you like) implementation using DART

The **DART** Framework

Designing for **A**ccele**r**ated **T**ranslation



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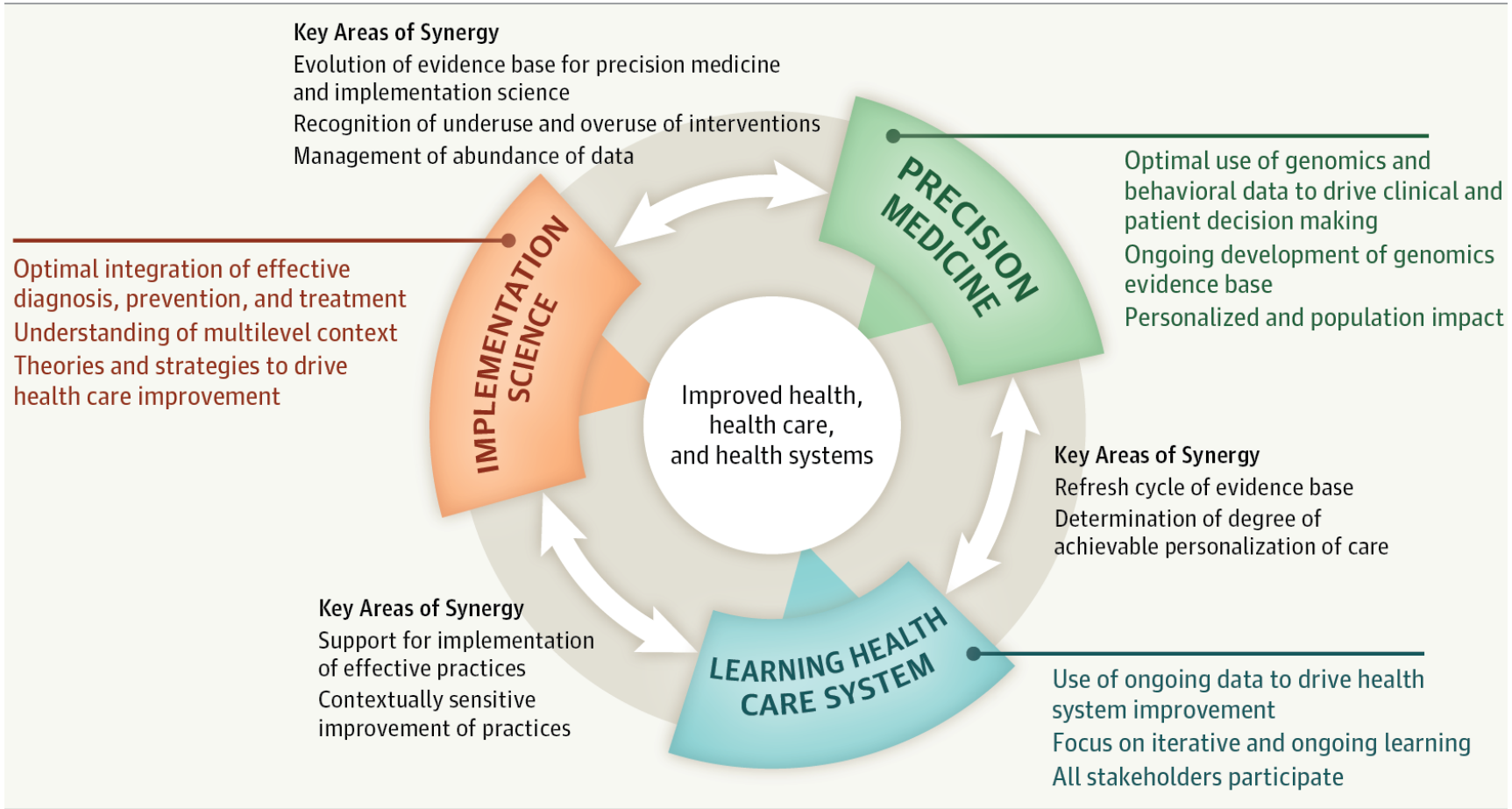
DART strategies to move things further, faster

	Current State: "Where We Are"	Optimal State: "Where We Want to Be"	Implementation or Improvement Strategies: "What It Will Take"
Meaningful Stakeholder Partnership	Research siloes	Team science	Develop partnerships early on across translational spectrum
	Restrictive samples	Citizen science	Harness power of public for scientific activities
	Disconnected from industry	Partnering with industry	Partner with those primed to bring innovations to market
Design Innovations for D&I	Pushing out innovations	Eliciting / meeting user demand	Understand user motives and context; demonstrate value add
	Researcher-driven	Human-centered design	Involve diverse group of end-users throughout development
	Efficacy over effectiveness	Robust, context-sensitive innovations	Better packaging of evidence for translation to practice / policy
Learning Healthcare System	Narrow use of evidence	Ongoing / efficient evidence review	Use existing data, rapid reviews, and Create-Trial-Sustain models
	Static delivery systems	Using iterative feedback	Give real-time feedback on key outcomes to providers
	Resistant to change	Nimble, change-oriented mindset	Train workforce in core concepts that apply across technologies

Synergies between implementation science, learning health care systems, and precision medicine



Chambers, Feero, Khoury.
JAMA 2016

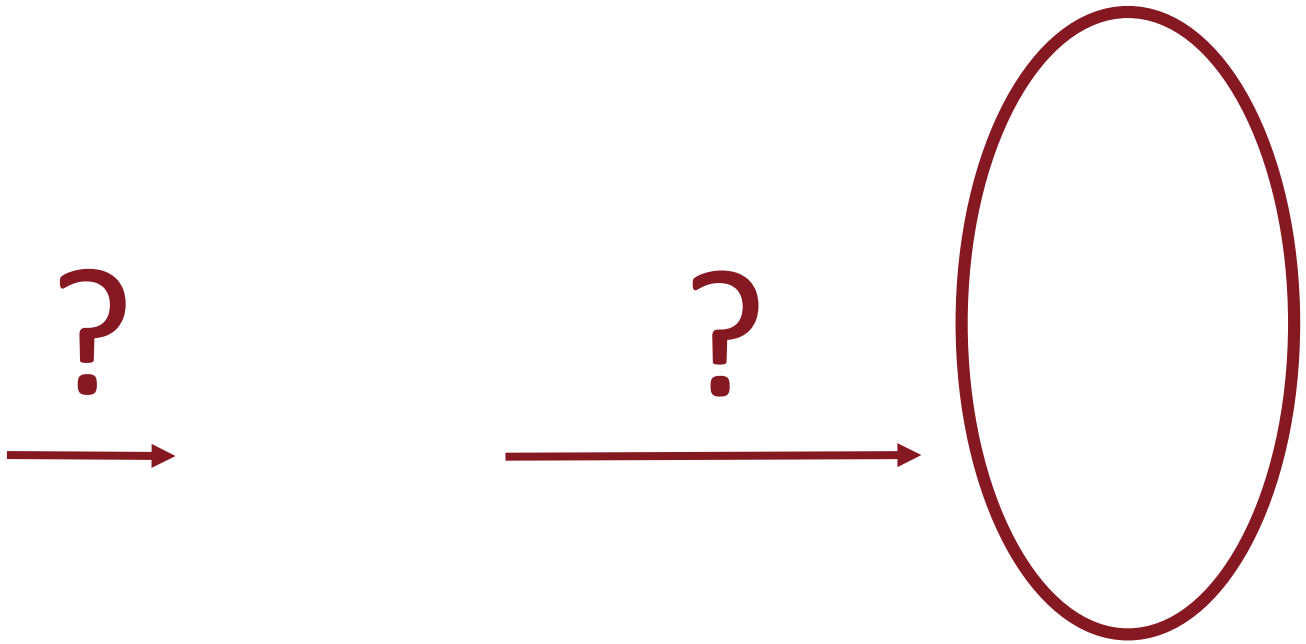
The Path for Precision ^Behavioral Medicine

E D. Green *et al*. *Nature* 2011

Applying genetics and genomics as tools to optimize behavioral interventions (McCaffery 2019)

Using known predictors of behavior, such as genetic predisposition, biology, environment, and past behavior to enhance treatment (Stump et al 2019)

The Path for Precision Behavioral Medicine



Applying genetics and genomics as tools to optimize behavioral interventions (McCaffery 2019)

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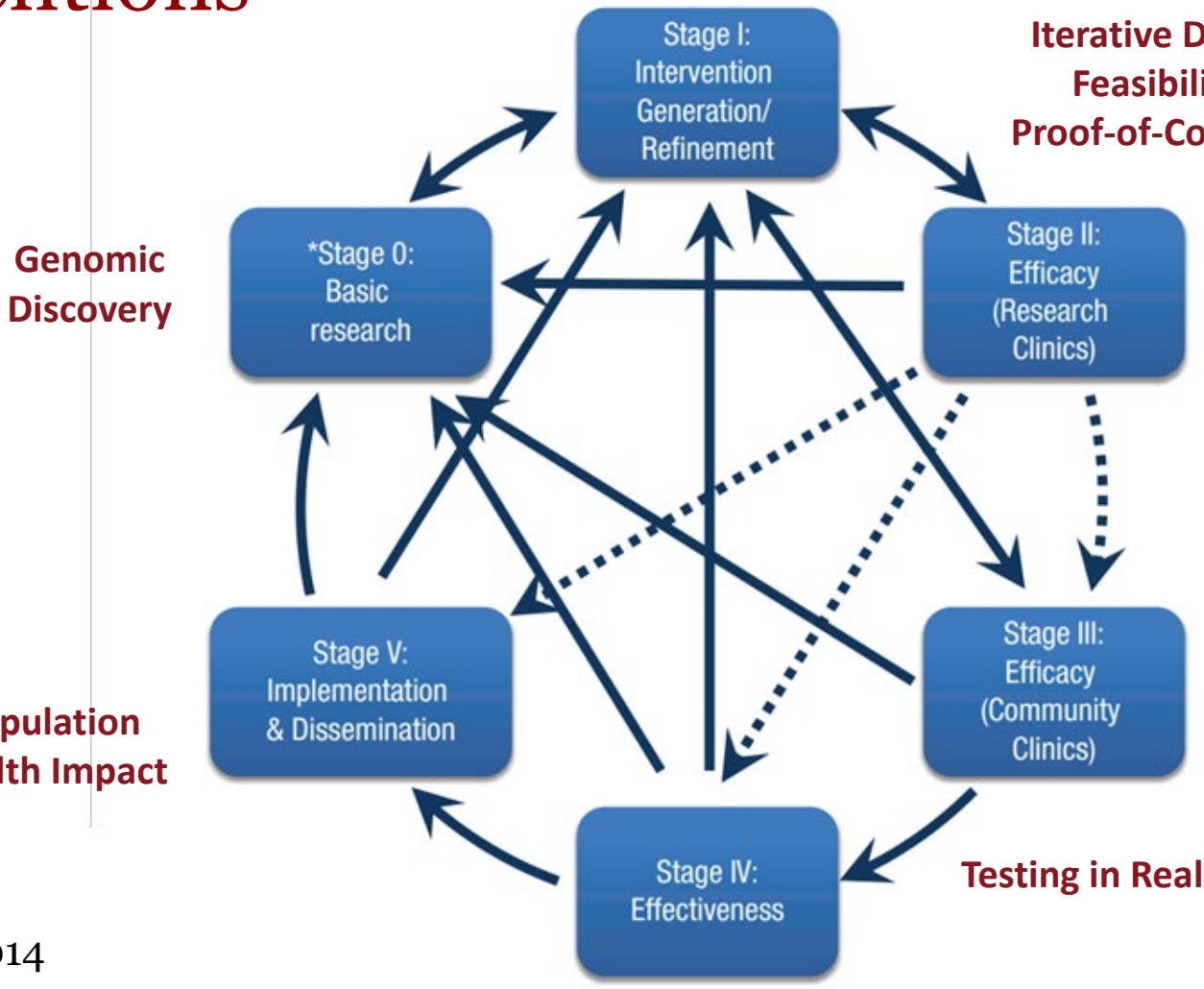
From Genomic Discovery to Genetically-Informed Behavioral Interventions

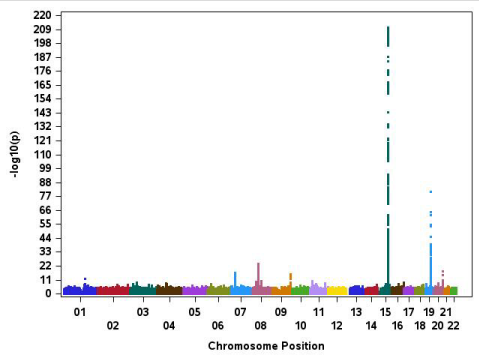
NIH Stage Model for Behavioral Intervention Development



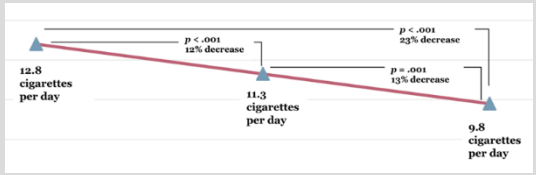
Onken, Carroll, *et al.* Clin Psychol Sci 2014

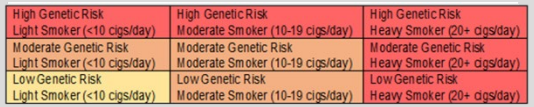
Genetics of Smoking: Bridging the Past, Present, and Future

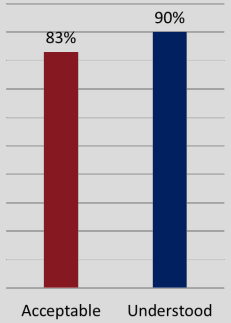
Genomic Discovery



Development and Proof-of-Concept Testing







Real-World Clinical Utility

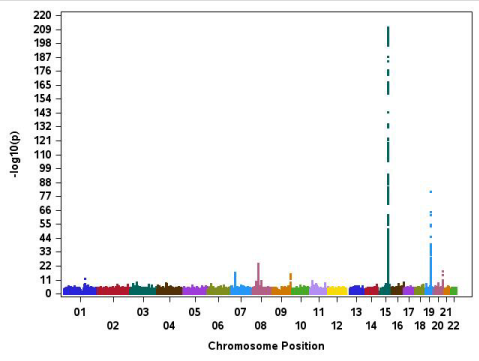
HOW YOUR GENETICS AND SMOKING IMPACT YOUR RISK FOR:

→ Lung cancer?
→ Other lung diseases?
→ Difficulty quitting smoking?

Stage 0: Basic Science → **Stage I: Intervention Generation/Refinement** → **Stage II-V: Efficacy to Implementation**

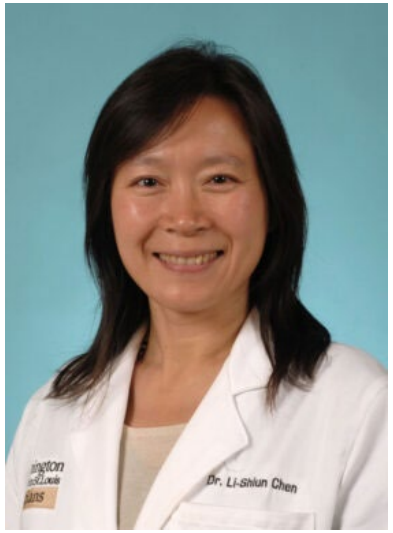
Genetics of Smoking: Bridging the Past, Present, and Future

Genomic Discovery



Stage 0: Basic Science

Laura J. Bierut, MD
Alumni Endowed Professor of Psychiatry



Li-Shiun Chen, MD, ScD, MPH
Associate Professor of Psychiatry

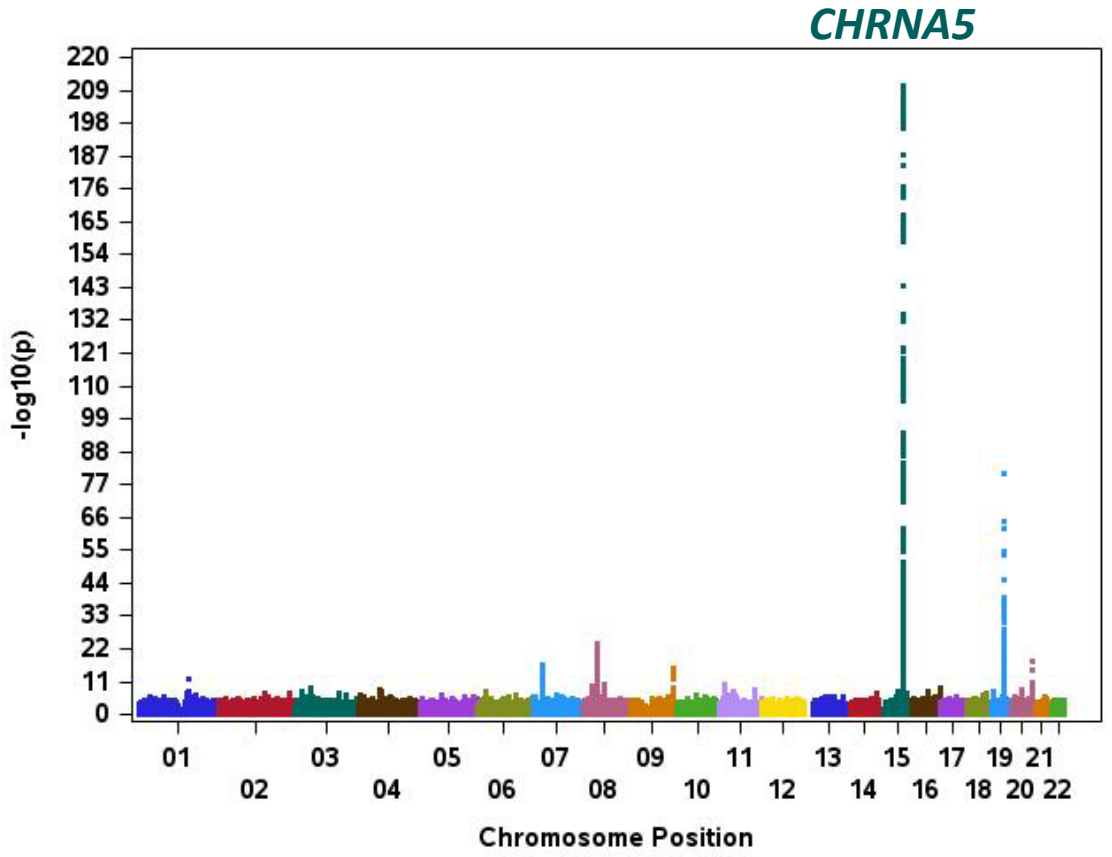
Prognostic significance of *CHRNA5* gene region

There is now evidence that variants in and near this gene have prognostic significance for:

- risk of smoking-related diseases
- likelihood of smoking cessation
- response to nicotine replacement therapy

Individuals with high-risk genetic variants:

- smoke more heavily
- have 2-fold increased risk for lung cancer
- develop lung cancer 4 years earlier
- quit smoking 4 years later
- have lower success with unassisted quit attempts



GSCAN Consortium., 2019

Genetics of Smoking: Bridging the Past, Present, and Future

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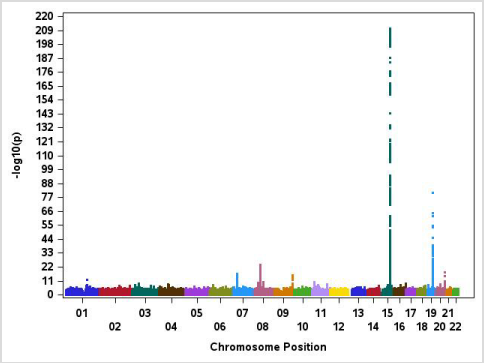

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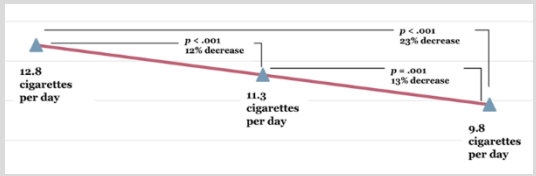
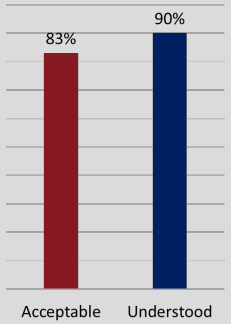


High Genetic Risk Light Smoker (<10 cigs/day)	High Genetic Risk Moderate Smoker (10-19 cigs/day)	High Genetic Risk Heavy Smoker (20+ cigs/day)
Moderate Genetic Risk Light Smoker (<10 cigs/day)	Moderate Genetic Risk Moderate Smoker (10-19 cigs/day)	Moderate Genetic Risk Heavy Smoker (20+ cigs/day)
Low Genetic Risk Light Smoker (<10 cigs/day)	Low Genetic Risk Moderate Smoker (10-19 cigs/day)	Low Genetic Risk Heavy Smoker (20+ cigs/day)



Stage 0: Basic Science → **Stage I: Intervention Generation/Refinement**

Iterative Design and Development

CANCER PREVENTION RESEARCH | RESEARCH ARTICLE

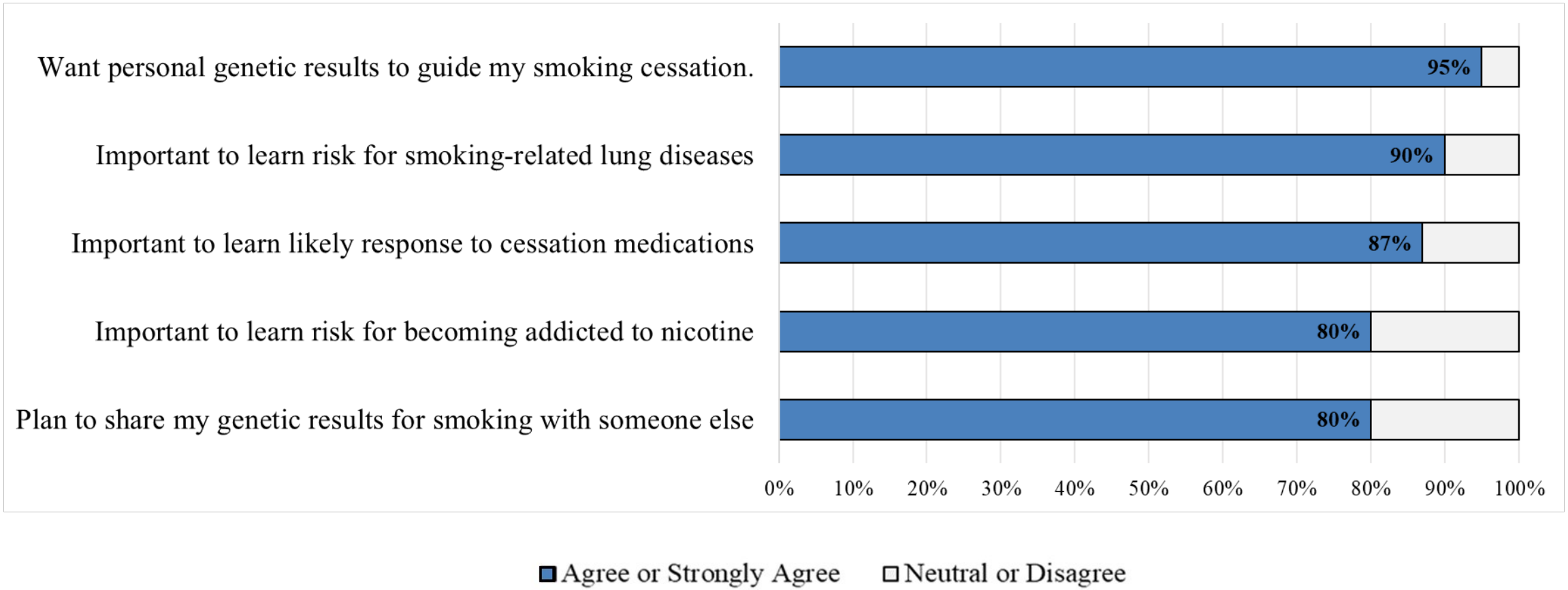
Participatory Design of a Personalized Genetic Risk Tool to Promote Behavioral Health

Alex T. Ramsey[1], Michael Bray[1], Penina Acayo Laker[2], Jessica L. Bourdon[1], Amelia Dorsey[1], Maia Zalik[1], Amanda Pietka[1], Patricia Salyer[1], Erika A. Waters[3], Li-Shiun Chen[1], and Laura J. Bierut[1]

Proof-of-Concept Testing

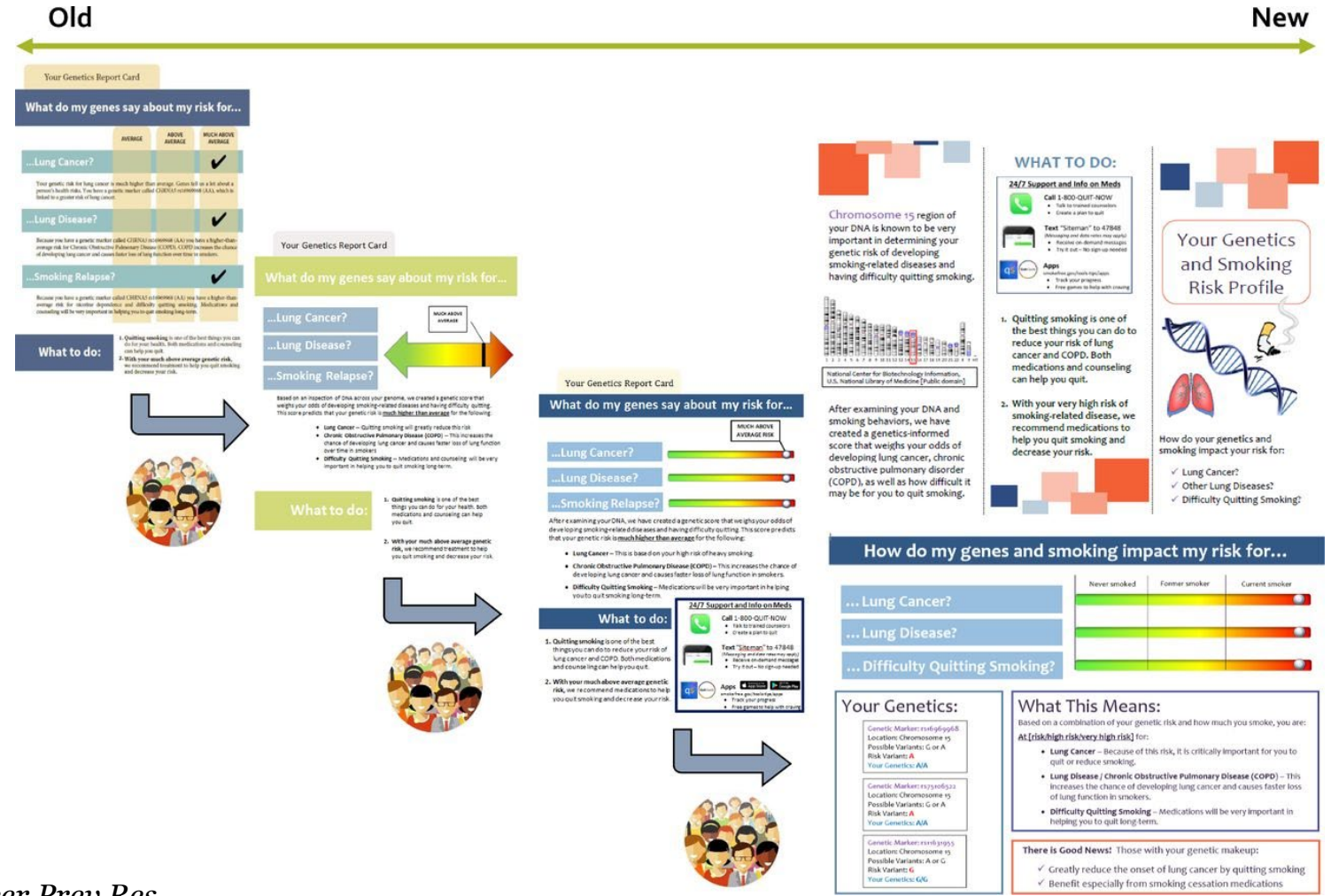
Ramsey, A.T., *et al.* (2020). Participatory design of a personalized genetic risk tool to promote behavioral health. *Cancer Prevention Research, 13*(7), 583-592.

High demand for smoking-related genetics (N=111 participants who smoke)



Ramsey et al. (2020). *Cancer Prev Res*.

Evolving design toward the "Genetics and Smoking *RiskProfile*"



Ramsey et al. (2020). *Cancer Prev Res*.

Iterative design and prototyping of *RiskProfile*

Introduction

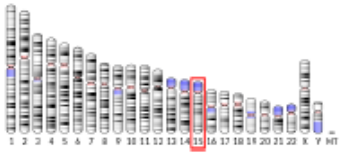
Your Genetics and Smoking Risk Profile

How do your genetics and smoking impact your risk for:

- ✓ Lung Cancer?
- ✓ Other Lung Diseases?
- ✓ Difficulty Quitting Smoking?

Brief Orientation

Chromosome 15 region of your DNA is known to be very important in determining your genetic risk of developing smoking-related diseases and having difficulty quitting smoking.



National Center for Biotechnology Information, U.S. National Library of Medicine [Public domain]

After examining your DNA and smoking behaviors, we have created a genetics-informed score that weighs your odds of developing lung cancer, chronic obstructive pulmonary disorder (COPD), as well as how difficult it may be for you to quit smoking.

Personalized Genetics, Risk Categorization, Interpretation and Framing

How do my genes and smoking impact my risk for…

- …Lung Cancer?
- …Lung Disease?
- …Difficulty Quitting Smoking?

Your Genetics:

Genetic Marker: rs16969968
Location: Chromosome 15
Possible Variants: G or A
Risk Variant: A
Your Genetics: A/A

Genetic Marker: rs75106522
Location: Chromosome 15
Possible Variants: G or A
Risk Variant: A
Your Genetics: A/G

Genetic Marker: rs11631955
Location: Chromosome 15
Possible Variants: A or G
Risk Variant: G
Your Genetics: G/G

What This Means:

Based on a combination of your genetic risk and how much you smoke, you are:

At very high risk for:

- **Lung Cancer** – Because of this risk, it is critically important for you to quit or reduce smoking.
- **Lung Disease / Chronic Obstructive Pulmonary Disease (COPD)** – This increases the chance of developing lung cancer and causes faster loss of lung function in smokers.
- **Difficulty Quitting Smoking** – Medications will be very important in helping you to quit long-term.

There is Good News! Those with your genetic makeup:

- ✓ Greatly reduce the onset of lung cancer by quitting smoking
- ✓ Benefit especially from smoking cessation medications

Quit Advice and Resources

WHAT TO DO:

24/7 Support and Info on Meds

Call 1-800-QUIT-NOW
- Talk to trained counselors
- Create a plan to quit

Text "Siteman" to 47848
(Messaging and data rates may apply)
- Receive on-demand messages
- Try it out – No sign-up needed

Apps
smokefree.gov/tools-tips/apps
- Track your progress
- Free games to help with craving

1. **Quitting smoking is one of the best things you can do to reduce your risk of lung cancer and COPD. Both medications and counseling can help you quit.**
2. **With your very high risk of smoking-related disease, we recommend medications to help you quit smoking and decrease your risk.**

Ramsey et al. (2020). *Cancer Prev Res*.

Iterative Design and Development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Proof-of-Concept Testing


CANCER PREVENTION RESEARCH

Research Article

Proof of concept of a personalized genetic risk tool to promote smoking cessation: High acceptability and reduced cigarette smoking

Alex T Ramsey, Jessica L Bourdon, Michael Bray, Amelia Dorsey, Maia Zalik, Amanda Pietka, Patricia Salyer, Li-Shiun Chen, Timothy B Baker, Marcus R Munafo, and Laura J Bierut

Ramsey, A.T., Bourdon, J.L., Bray, M., Dorsey, A., Zalik, M., Pietka, A., Salyer, P., Chen, L-S., Baker, T.B., Munafò, M.R., & Bierut, L.J. (2021). Proof of concept of a personalized genetic risk tool to promote smoking cessation: High acceptability and reduced cigarette smoking. *Cancer Prevention Research, 14*(2), 253-262.

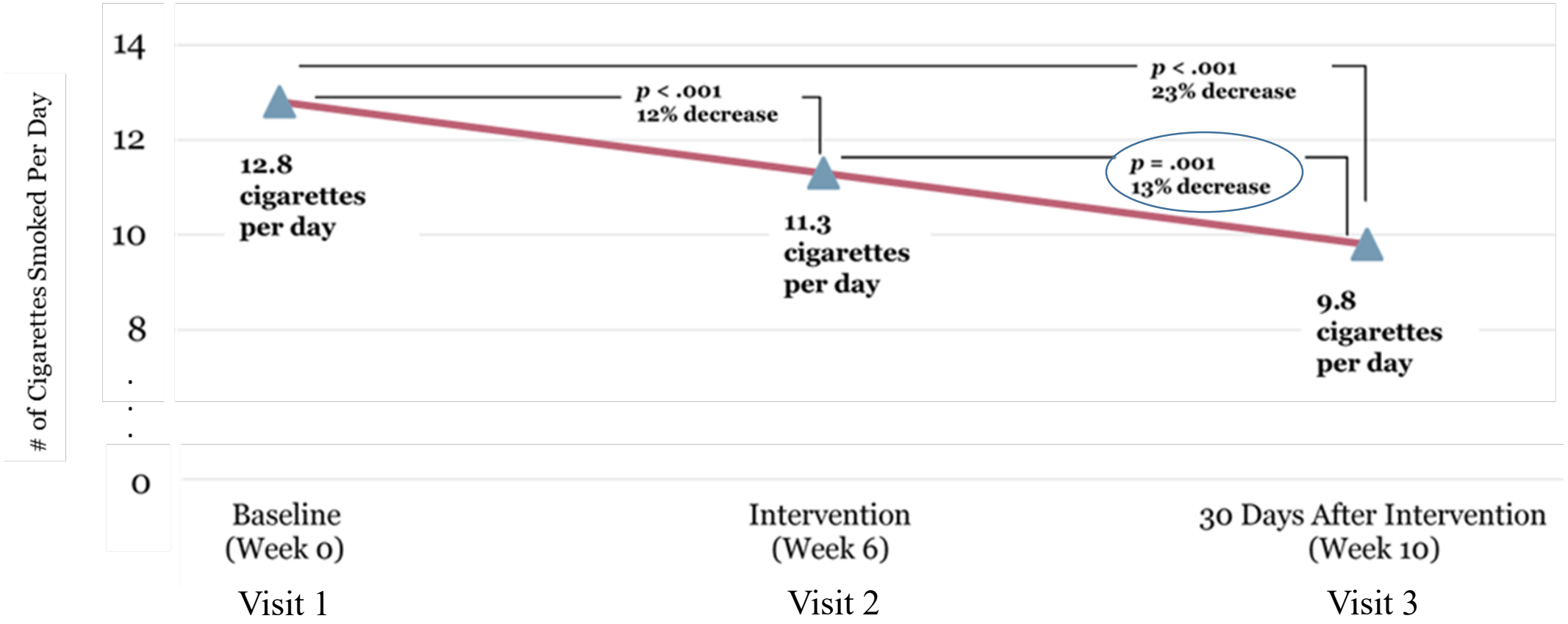
RiskProfile was acceptable and well-understood

- Acceptability of Intervention
  - 83% of participants rated the intervention as highly acceptable
- Decision Regret
  - 99% of participants affirmed that they would make the same decision again to receive *RiskProfile*
- Comprehension and Recall of Results
  - Over 90% at follow-up reported understanding *RiskProfile* moderately to extremely well
- Perceived Intervention Utility
  - 91% found the tool useful-to-extremely useful overall

N=108 participants who smoke
58% White, 34% Black, 7% Other
35% High school diploma or less

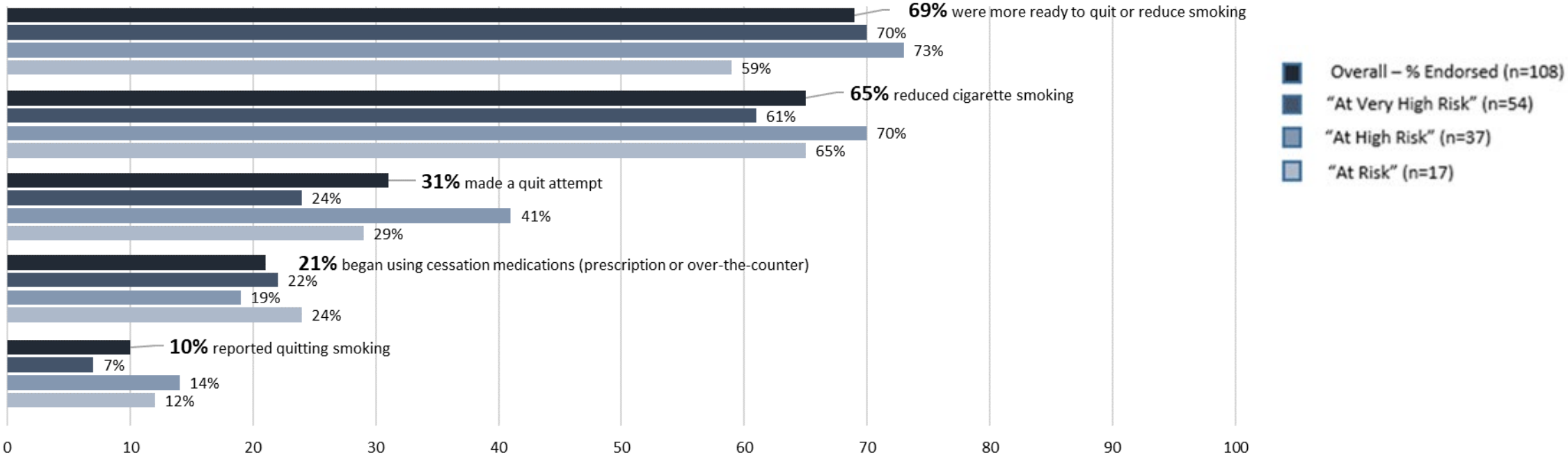
Ramsey et al. (2021). *Cancer Prev Res*.

Reduced smoking after receiving *RiskProfile* (n=108)



Ramsey et al. (2021). *Cancer Prev Res*.

Smoking-related behavior change by *RiskProfile* status (n=108)

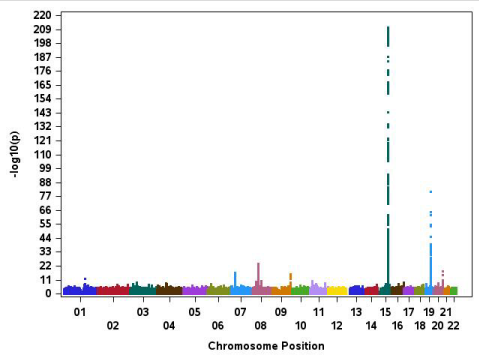


No clear differences by risk level

Ramsey et al. (2021). *Cancer Prev Res*.

Genetics of Smoking: Bridging the Past, Present, and Future

Genomic Discovery



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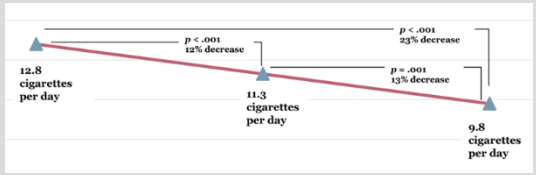

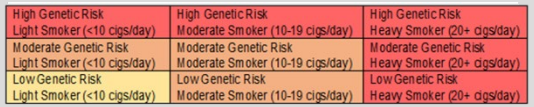

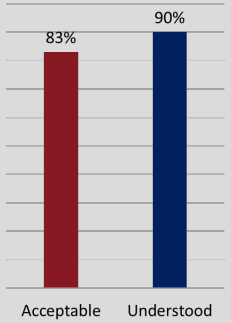

Real-World Clinical Utility

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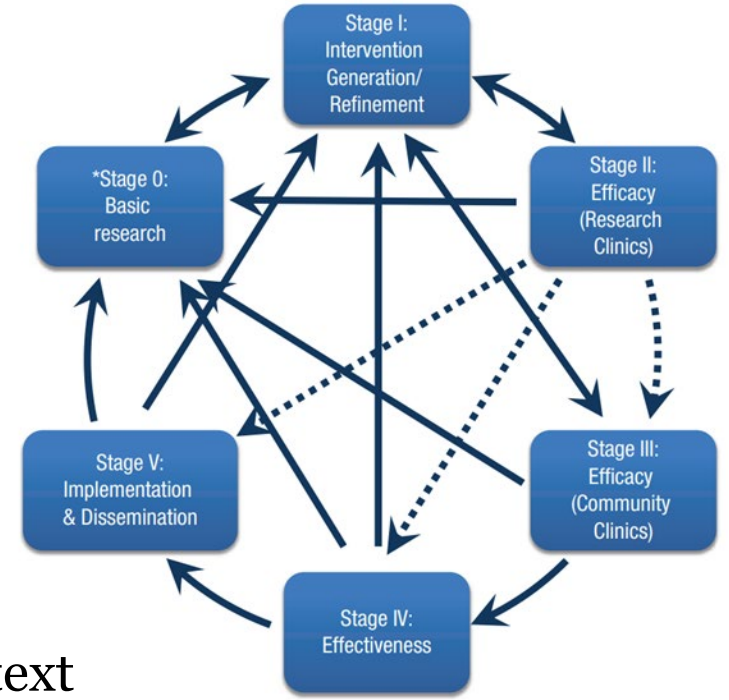
Stage 0: Basic Science → **Stage I: Intervention Generation/Refinement** → **Stage II-V: Efficacy to Implementation**

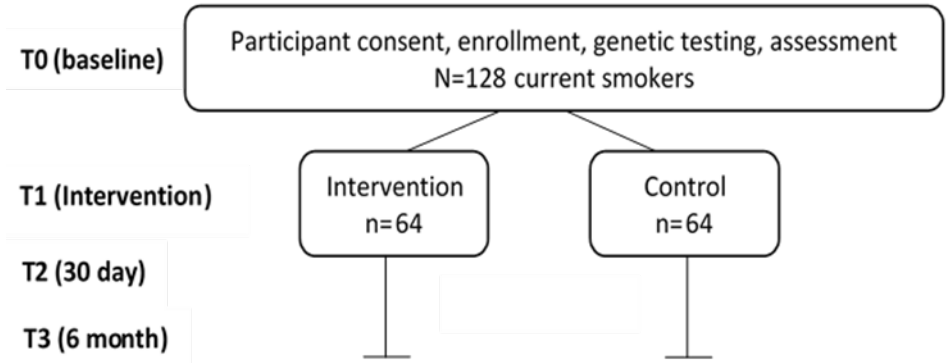
Learning simultaneously across the (iterative) research pipeline

Are genetically-informed interventions for smoking ready to proceed to:

- Next stage of innovation development? YES
  - Developing/refining polygenic risk scores
  - Studying behavior change mechanisms
- Clinical trial testing? YES
  - RCT with active control and longer-term follow-up
  - Establishing effect sizes
- Implementation research? YES
  - Hybrid Type 1 studies: Gather info on implementation context
  - Understand multi-level barriers, facilitators, acceptability, feasibility
  - Adapt for telehealth, behavioral health, lung cancer screening, and primary care settings

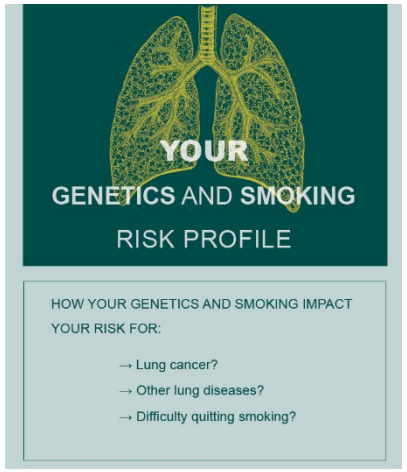


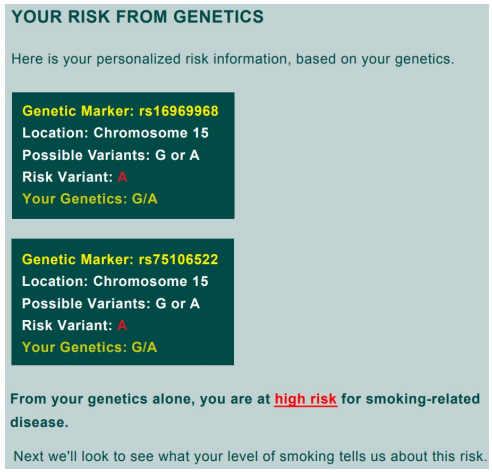
Fully-Remote Parallel-Group RCT (current NIDA R34)

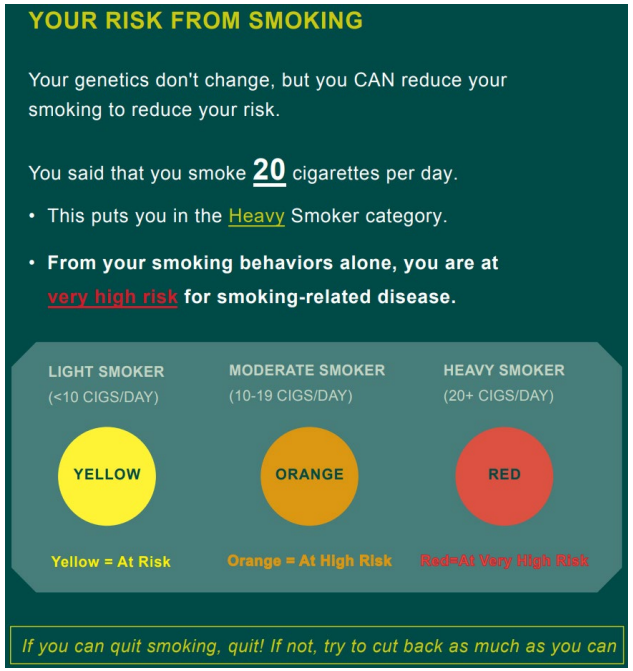


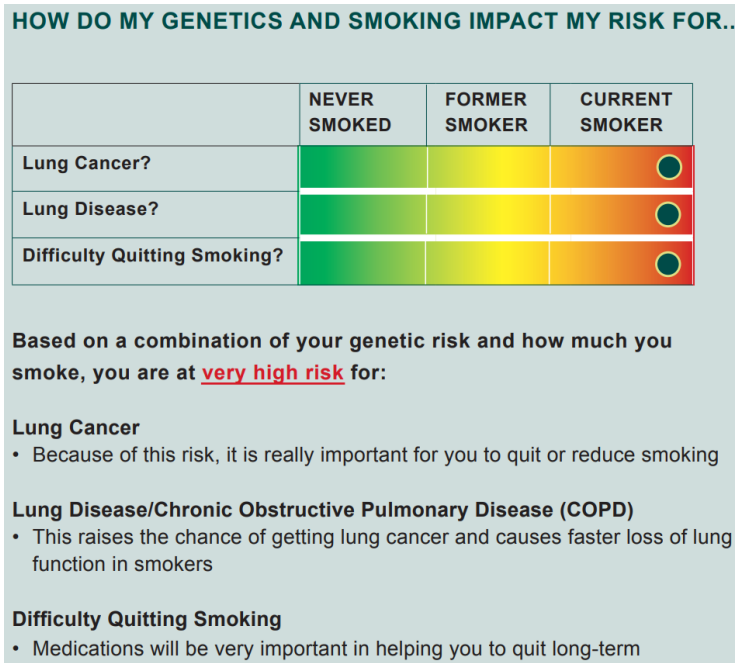
Control = Brief Cessation Advice

Intervention = Brief Advice + *RiskProfile*

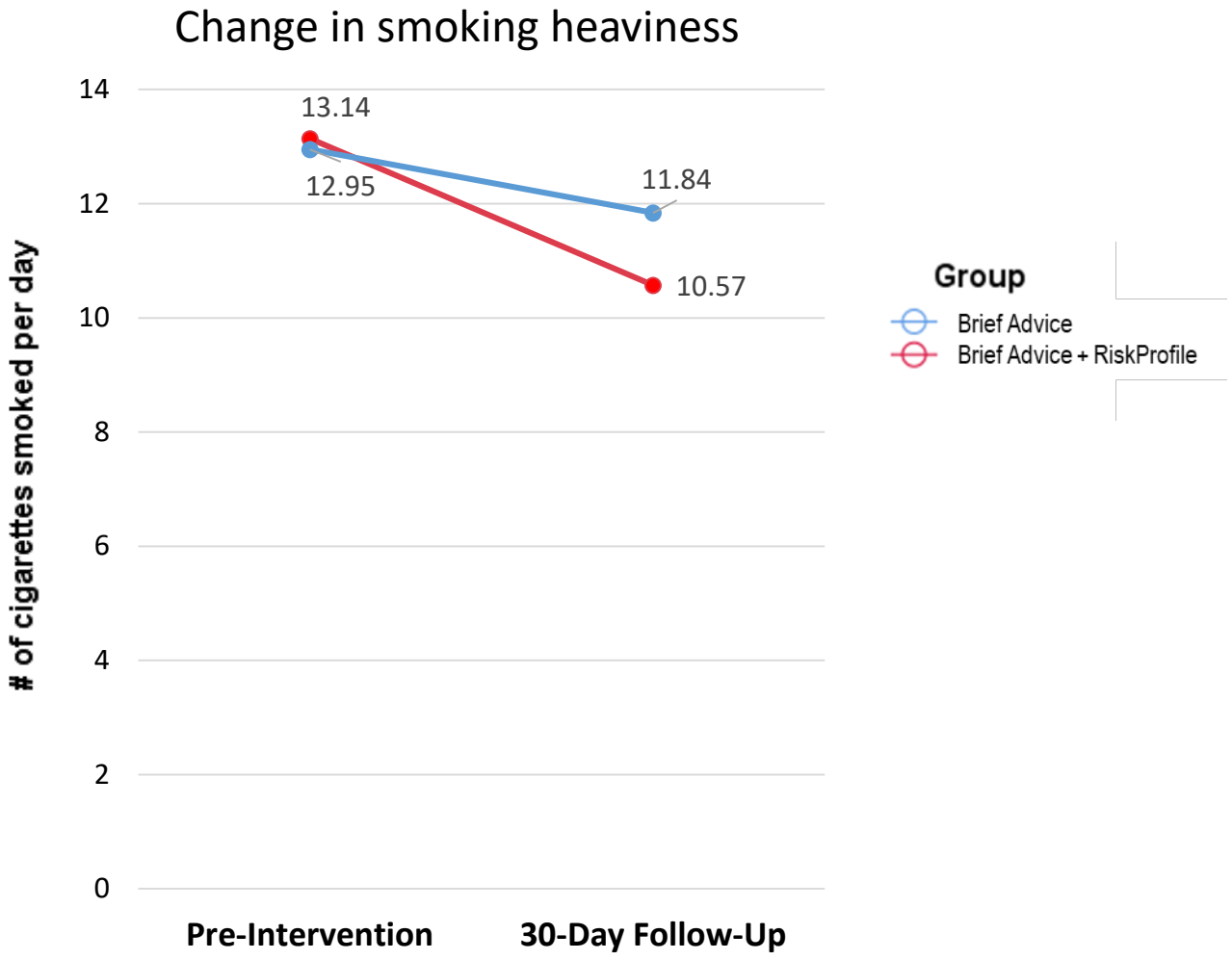


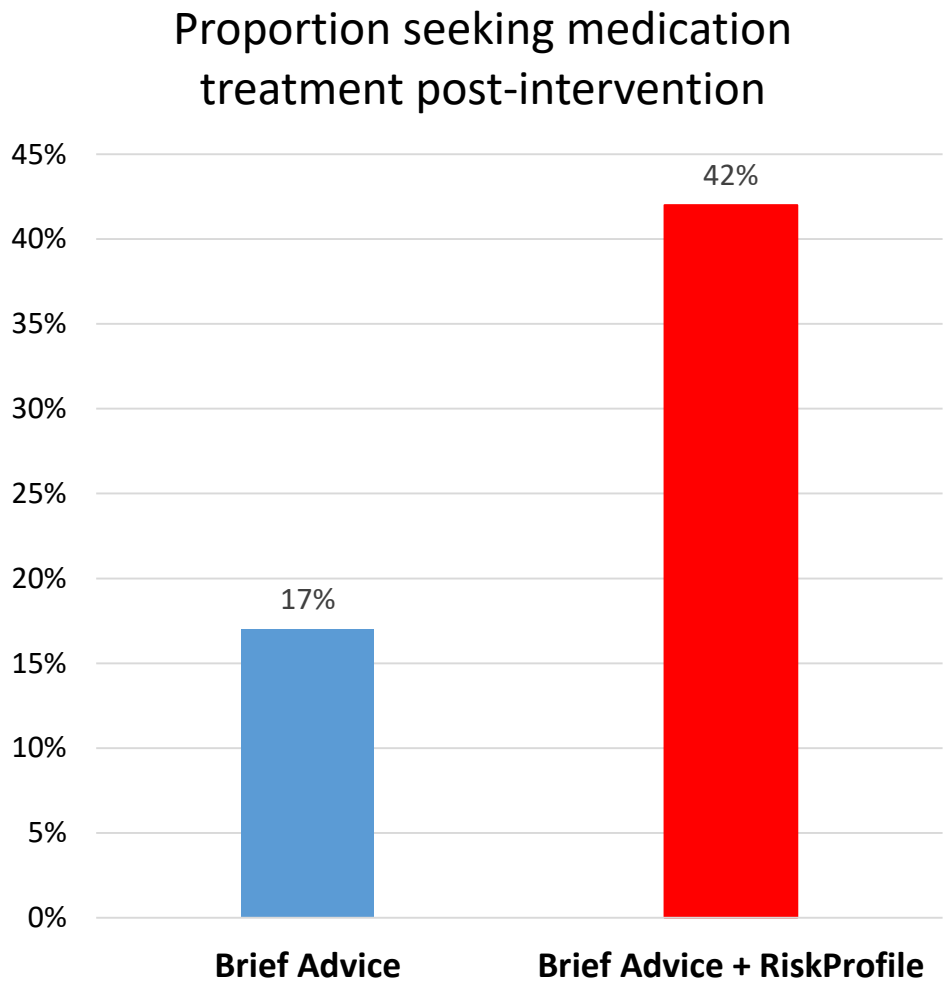






Early results suggest decrease in smoking after *RiskProfile* (n=61)





Large-scale cluster RCT in primary care (pending NCI R01)

Aim:

To test the impact of a personalized risk feedback tool on ***physician ordering*** and ***patient receipt*** of lung cancer screening and smoking cessation treatment

Goal:

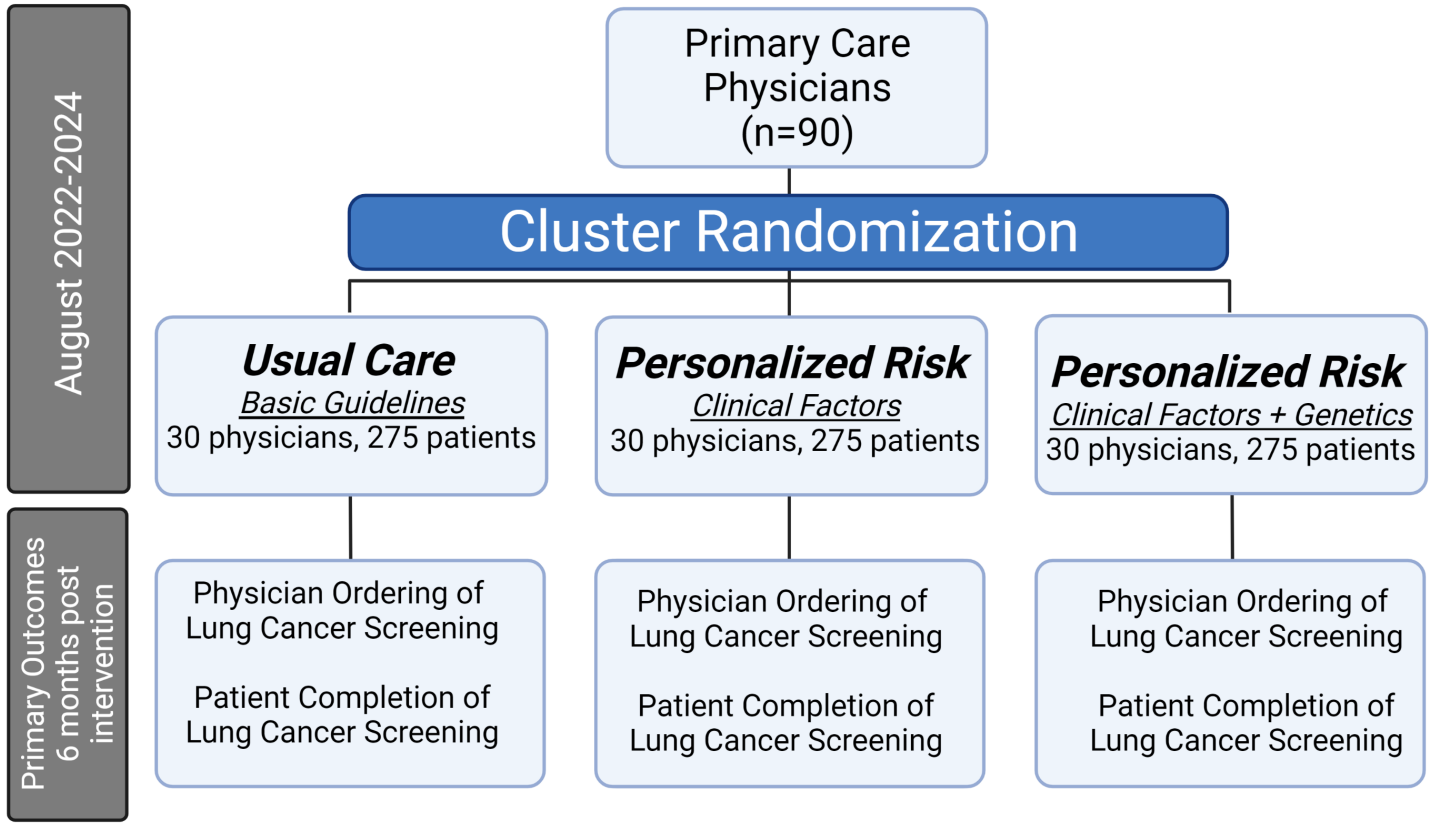
To improve primary and secondary prevention of smoking-related lung cancer

Approach:

Comparing 3 Arms

Arm 1: Usual Care	Standard of care, brief advice, and guideline awareness
Arm 2: *RiskProfile-Clin*	Multilevel intervention based on clinical factors only
Arm 3: *RiskProfile-Gen*	Multilevel intervention based on clinical and genetic factors

3-arm cluster RCT comparing usual care to multilevel precision health intervention, with and without genetics



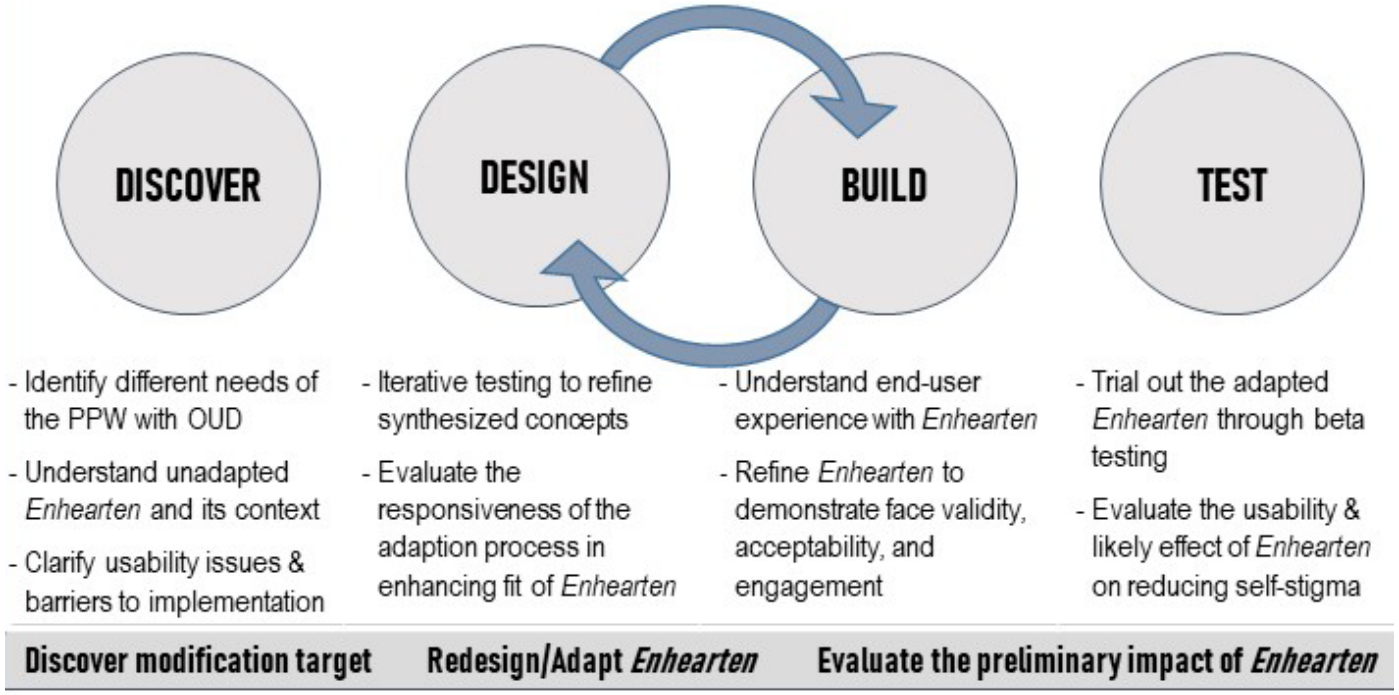
Usual Care: Screening and treatment recommendation as usual, with USPSTF guideline awareness

***RiskProfile-Clin*:** Risk feedback based on demographic and clinical factors alone using established PLCOm2012 model

***RiskProfile-Gen*:** Risk feedback based on clinical (PLCOm2012) plus genetic factors (ancestry-specific polygenic risk scores)

Digital intervention to reduce self-stigma among pregnant and postpartum women with opioid use disorder (pending NIDA SBIR)

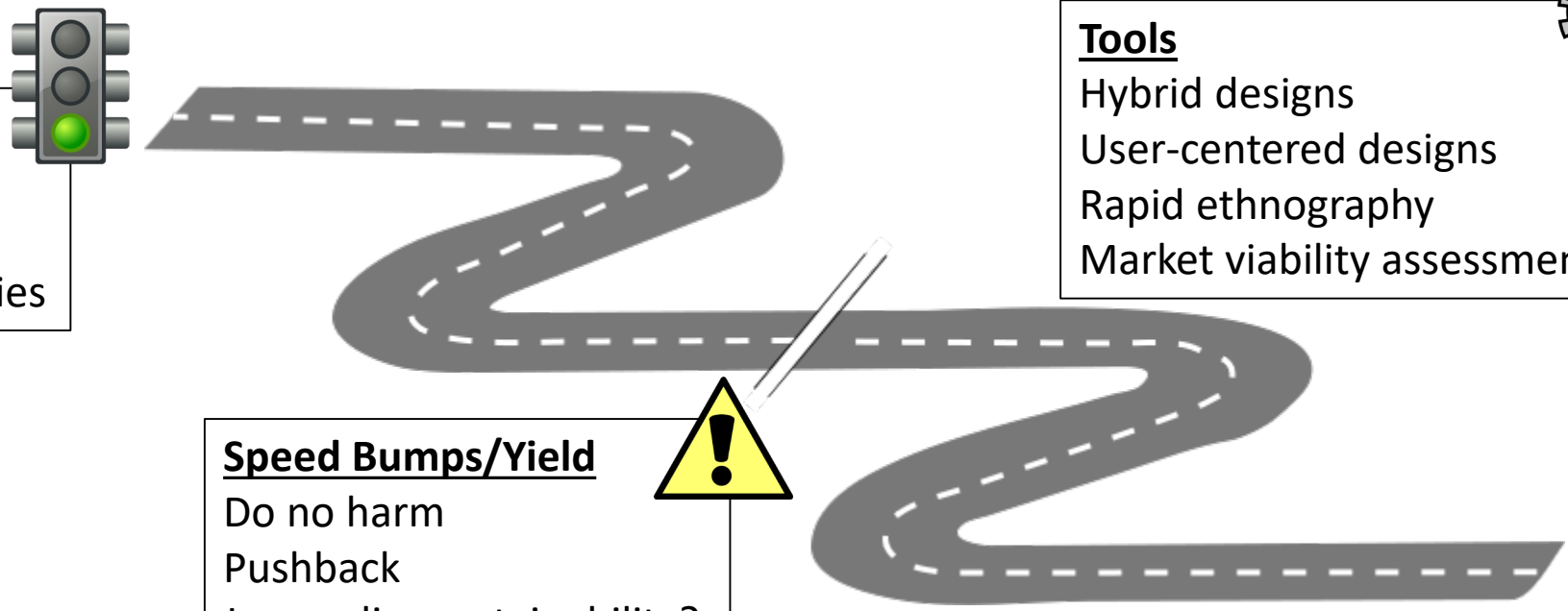
Phase 1 (1 year)
Discover, Design/Build, Test (DDBT) Framework



Phase 2 (2 years)
Additional DDBT

then
RCT to test adapted digital intervention

Need for Translational Speed (with appropriate guardrails)



The Why
Grant mechanisms
Global pandemics
Healthcare inequities

Tools
Hybrid designs
User-centered designs
Rapid ethnography
Market viability assessment

Speed Bumps/Yield
Do no harm
Pushback
Jeopardize sustainability?
Risk further inequities?

Guidance
Align with local needs
Move at speed of trust (earned)
Measure and report on speed!!!

Methodological Gap:
Systematically measuring and reporting on the pace of research translation and understanding the influences on and impact of implementation speed

Proctor, Ramsey, et al, under review

Speed… who cares about that?

Stakeholder perspectives and selected priorities on the speed of research translation	
Stakeholders	**Perspectives and priorities (sample questions)**
Intervention developers, trainers, and purveyors	How long until the innovation is adopted?
Clinicians	How long will the innovation take to learn? How long to reach competence? When can the innovation be used?
Clients and patients	How long until the innovation is available? How long until improvement is seen?
Administrators	How long is the change process? How quickly will new innovation become routine?
Payers	How long until return on investment?
Policy makers	How do current or proposed policies affect the speed of research translation?
Communities	How long until users of the innovation are reached? How long until coverage rates are adequate?
Advocates	Does rapid research affect health equity? How long until equity is realized?
Researchers (**Current****)**	How long does it take to translate evidence to practice?
Researchers (**Proposed****)**	How long will each stage of research translation take for this innovation? How can we better measure the speed of change? What factors will impact speed? What strategies will enhance speed? How do we increase speed for disadvantaged groups? What effects did speed at both the translational research and applied implementation levels have on overall impact of the innovation?

Proctor, Ramsey, et al, under review

Speed… in reference to what?

Potential referents of speed	
Speed of what?	**Examples**
Completing phases of the implementation process	Once we complete the readiness planning stage, how soon do we begin hiring and training the staff needed for implementation?
Attaining implementation outcomes	How quickly can we achieve 50% screening uptake by physicians?
Achieving service system outcomes	How long will it take for us to increase patient-centeredness reports by 20%?
Attaining clinical and population-level outcomes	How quickly can society reach herd immunity via vaccine rollout?

Proctor, Ramsey, et al, under review

Speed… how do we measure it?

Measurement of Speed	
Domains for Measuring Speed	**Example Metrics**
Speed in the Implementation Process	
Time elapsed to achieve predefined implementation milestone	Number of days from starting provider training to first person receiving the intervention
Time elapsed to attain predefined outcome (implementation, service system, clinical outcomes)	Number of months to attain 60% of eligible providers delivering the intervention following clinic adoption
Implementation progress between predefined time periods	Number of implementation steps completed or outcomes attained in 6 months
Rate of progress (or changes in slope) over time or between milestones	% increase in sites adopted in first 6-month period vs. second 6-month period Visual depiction (i.e., curve) of % increase in providers engaged 6 months prior to readiness assessment vs. 6 months subsequent to readiness assessment
Pace of iterative development or improvement	Time elapsed (in days) from start to end of 1st PDSA cycle, 2nd PDSA cycle
Speed in the Translation of Research	
Time spent within a translational stage (and time saved in subsequent iterations within the translational stage)	Number of months to develop first versus second iterations of intervention
Time to advance from one translational stage to another	Number of months from intervention development to efficacy testing in real-world settings (e.g., from Stage I to Stage III in NIH Stage Model for Behavioral Intervention Development)

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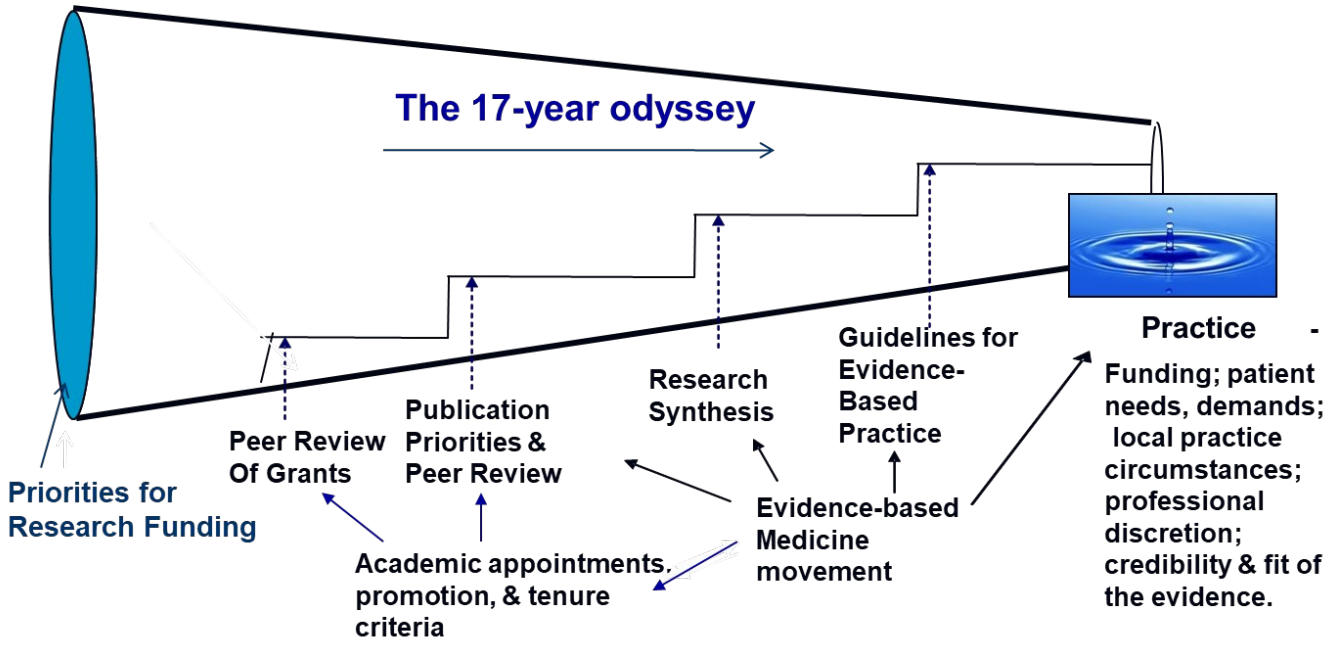
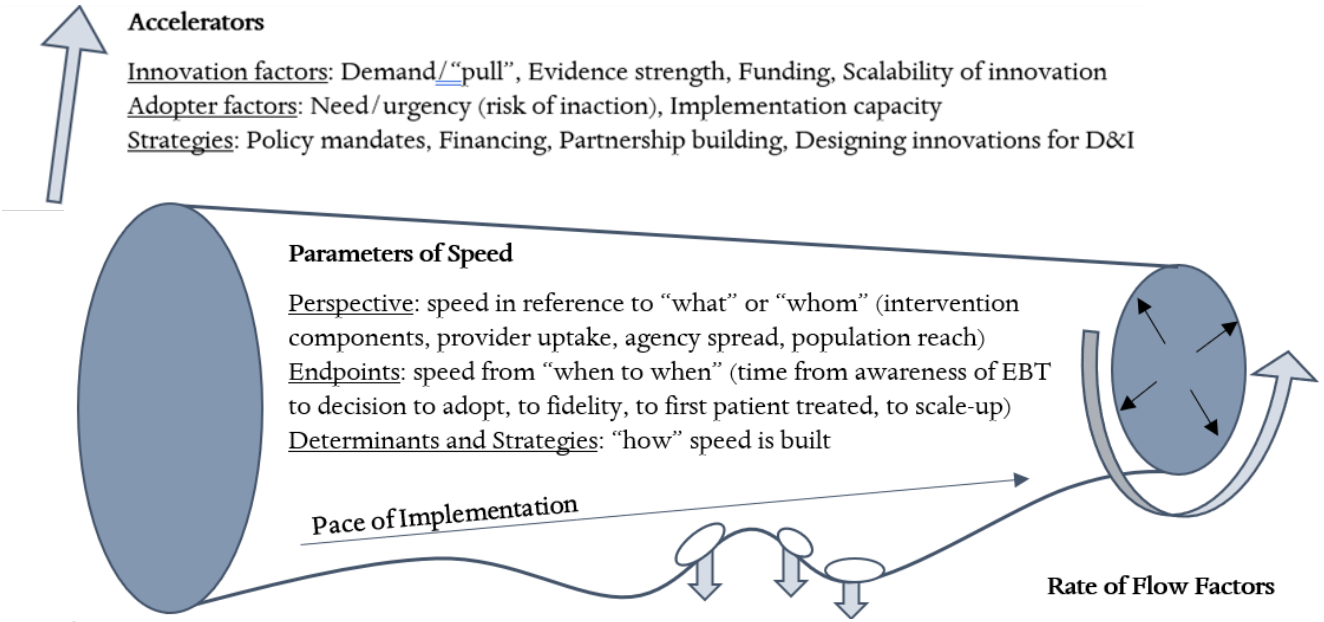
Can we expedite the 17-year odyssey?



Framework to Assess Speed of Translation (FAST)
Determinants of implementation pace



Effects of Speed

Faster attainment of desired outcomes:
- Implementation outcomes
- Service outcomes
- Clinical outcomes
- Population-level outcomes
- Health equity

Faster completion of implementation phases
Need heightened attention to protect against potential risk of clinical harms or disruption

↑ Relevance of innovation
↑ Stakeholder engagement
↓ Implementation barriers (secular changes)
↓ Time until public health impact

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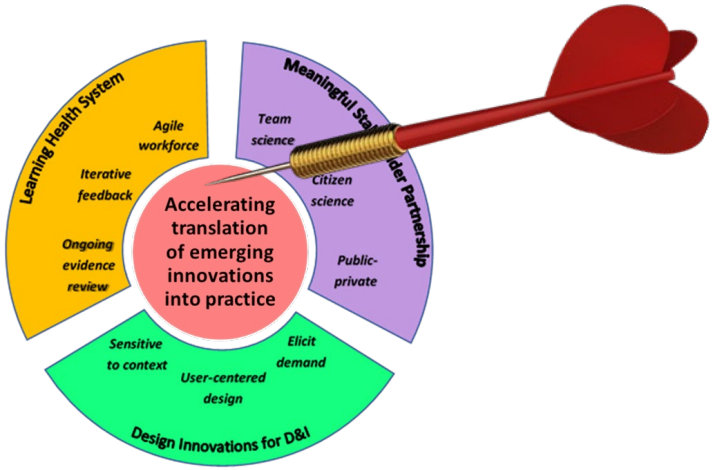
Key Take-Aways



- DART can serve as guide to assess and accelerate implementation readiness.
- Evaluate and address factors beyond efficacy/effectiveness – demand, risk ratio, costs – to accelerate.
- When possible, learn and advance science simultaneously along the translational research pipeline.
- Genomically-informed and technology-based interventions are excellent, multidisciplinary test beds.
- Measure and report on implementation speed – an underexplored area.
- Designing for D&I, meaningful partnerships, and learning health systems can help us go further, faster.

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Thank You!

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