New Approaches and Challenges to Genetic Testing for Cancer Risk

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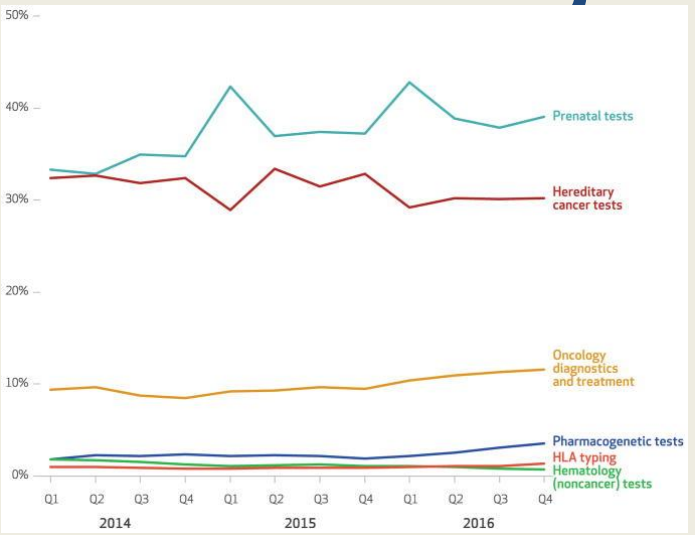
- *The speaker has no conflicts to disclose*
- *The speaker has current and prior patents bearing on BRCA2, targeting nucleotide excision repair*
- *The speaker is a founder of AnaNeo Therapeutics*
- *These do not bear on current presentation*
- *The speaker does not endorse any of the commercial labs mentioned in the presentation.*

New Approaches and Challenges to Genetic Testing for Cancer Risk

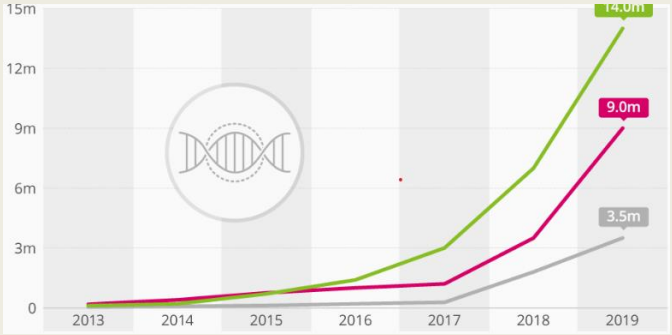
- **Challenges to Clinic Based Engagement**
  - Peaking volume of clinical testing
  - Direct To Consumer labs: (SNPs, specific variants; exomes/genomes; ancestry)
    - "Consumer Initiated Testing" models
    - "Third Party Interpretation" (TPI) of raw genomic data (educational purposes only)
  - Regulatory Approaches
- **Novel Clinical Approaches**
  - Founder mutation screening in genetic isolates
  - Facilitated diffusion (Cascade) Testing

Why focus on clinic-based cancer genetic testing?…

- Testing via clinical practice proven to decrease mortality
- Despite 2 decades of enthusiasm claims for medical cancer genetic tests flat during recent period
- At same time , Direct To Consumer and Ancestry tests up 27M with one company FDA approved also to offer a diagnostic test
  - However, One DTS WGS company suspended U.S. ops in 2019; another offering SNPs laid off 100 employees in 2020; sales for that company and an ancestry company down in 2019; shift to use databases already in hand
- Rise of consumer initiated tests; web site lists >120 companies



https://www.healthaffairs.org/doi/10.1377/hlthaff.2017.1427



https://www.statista.com/chart/17023/commercial-genetic-testing/

https://www.theverge.com/2022/3/31/23002953/home-testing-letsgetchecked-genetic-sequencing-veritas

Offit et al, 2022 (in revision)

Exploring the Current Landscape of Consumer Genomics: Proceedings of a Workshop National Academies of Sciences, Engineering, and Medicine; 2019 PMID: 32721146

- https://redcap.link/2be68lej
- 87.8% had counseled patients with DTC findings in the past 3 years
  - (~75% counseled 1-10 patients, ~25% counseled more than 10 patients)
- 35% had counseled on "liquid biopsy" findings

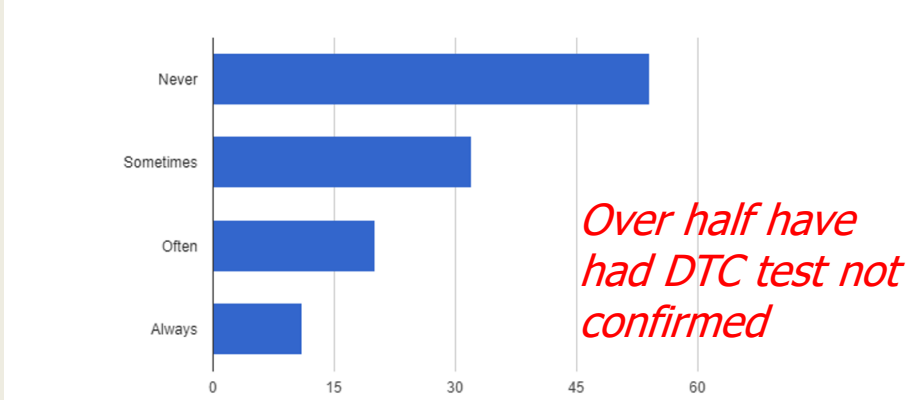
Healthcare professionals' experience with DTC/ CIT

Responses: n=139

Healthcare profession breakdown

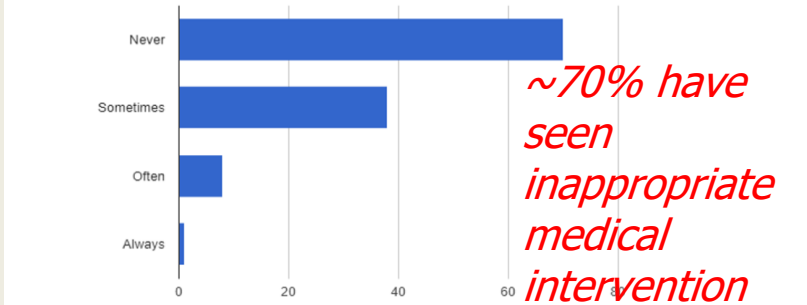
- Genetic Counselor (88.5%)
- MD/DO (5.0%)
- Other (6.5%)

Patient's result from DTC/CIT was not confirmed when repeated in a reference lab (n=117)



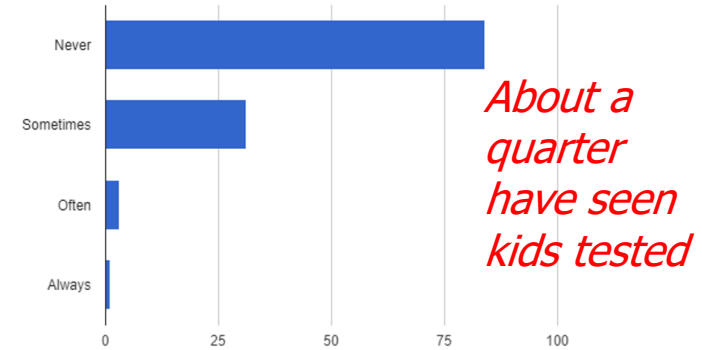
Over half have had DTC test not confirmed

Cases where DTC/CIT testing led to inappropriate medical care (e.g., prophylactic surgery, insufficient screening or follow-up) (n=117)



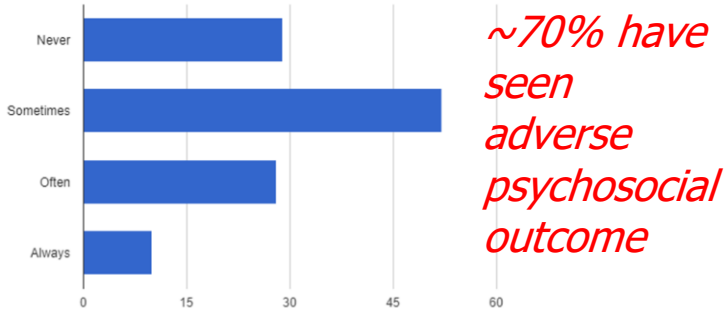
~70% have seen inappropriate medical intervention

Cases of DTC/CIT testing of a minor-aged child (n=119)



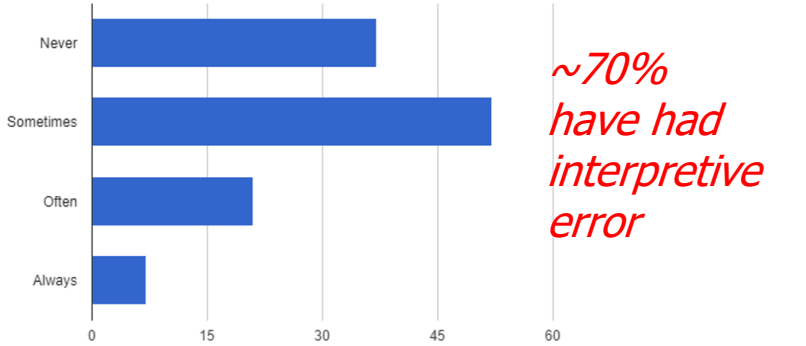
About a quarter have seen kids tested

Cases where DTC/CIT testing led to adverse psychosocial event that could have been ameliorated by pre-test genetic counseling (e.g., extreme distress or anxiety) (n= 119)



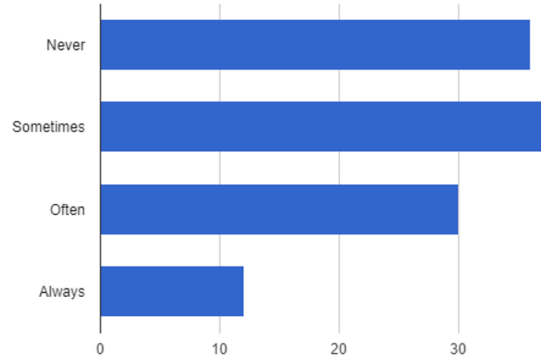
~70% have seen adverse psychosocial outcome

Patient's DTC/CIT analytic interpretation of the test result was incorrect (e.g., variant was reported but interpretation of significance or actionability was incorrect) (n=117)



~70% have had interpretive error

Patient's derived result from DTC/CIT was run through a third-party algorithm or database (e.g., for raw data interpretation) and produced a result that could not be confirmed in a reference lab (n=115)



~65% have seen error from Third Party Interpretation

2022 in progress

Unpublished not for distribution

Opportunity for increased regulatory oversight of LDTs and DTC,CIT

- During COVID-19 pandemic FDA permitted manufacturers to distribute validated tests prior to FDA authorization.
- HHS determined that the FDA will not require premarket review of laboratory developed tests (LDTs), including cancer tests.
- In response, the **Verifying Accurate Leading-edge IVCT (in vitro clinical test) Development Act of 2021 (VALID ACT)**
  - Bi-partisan/Bi-cameral ; Burr and Bennet in Senate: Federal proposal to redefine regulatory oversight of IVCTs, including those directed to consumers seeking tests for cancer predisposition or molecular diagnosis,
  - ***VALID Act would unequivocally give FDA authority to regulate "in vitro clinical tests (IVCTs)" i.e. all in vitro diagnostics (IVD) and Lab Developed Tests (LDTs) via a new risk-based framework to calibrate regulatory authorities between FDA and CMS.***

Suggested Amendments:

- Ensure premarket review to ensure analytic and clinical validity of tests that will determine medical interventions.
- Include raw genomic data reports that bear on health as falling within purview of FDA review.
- Specify mechanisms for healthcare workers to report cases of genomic test-related patient harm to the FDA
- Prohibit regulatory exclusions of tests claimed to be for "educational" purposes if they are viewed by professional bodies as generating clinically actionable findings.
- Harmonize provisions of S.1666, the Verified Innovative Testing in American Laboratories (VITAL) Act of 2021, distinguishing the special exigencies of COVID-19 testing compared to non-COVID-19 LDT's such as cancer risk and diagnostic genomic assays.

Other Regulatory Considerations

- Provide consumers with assurances of professional proficiency of health care providers ordering and interpreting consumer genomic tests

Offit, Sharkey 2022 et al. *in revision*

Pending Regulatory Reform, what are likely cost effective strategies to implement clinic based cancer genomic screening?

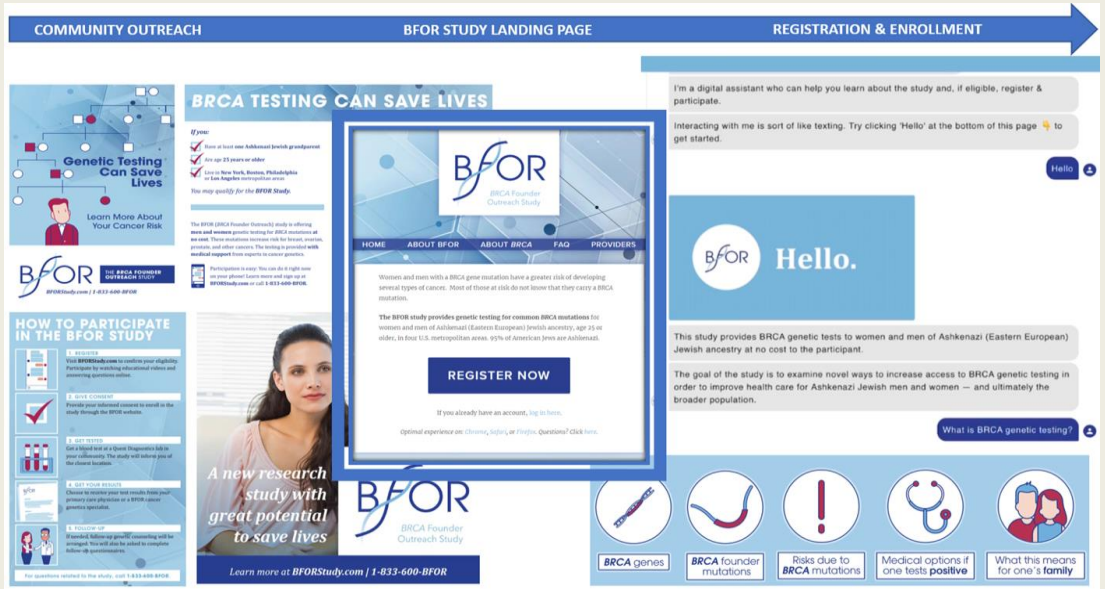
- Founder population testing
- Tumor normal followed by cascade testing

Targeted *BRCA1/2* Population Screening Among Ashkenazi Jewish Individuals Utilizing a Web-enabled Medical Model: An Observational Cohort Study

GENET MED. 2022 MAR;24(3):564-575. PMID: 34906490.

Morgan KM, Hamilton JG, Symecko H, Kamara D, Jenkins C, Lester J, Spielman K, Pace LE, Gabriel C, Levin JD, Tejada PR, Braswell A, Marcell V, Wildman T, Devolder B, Baum RC, Block JN, Fesko Y, Boehler K, Howell V, Heitler J, Robson ME, Nathanson KL, Tung N, Karlan BY, Domchek SM, Garber JE, Offit K.

- We offered on line testing using a medical model to >4,000 individuals of Ashkenazi ancestry in N.Y. Phillie, L.A., Boston
- During registration, **64.9%** of participants selected a BFOR provider and 35.1% of participants nominated their primary care provider (PCP)
- Upon nomination, **40.5%** of PCP invitations to disclose results were accepted; for the remainder, results were disclosed by the BFOR team



- Participant knowledge following digital education comparable to traditional pre-test counseling
- Over a quarter >65 years old; older age not barrier to a web-based initiative
- **Challenges** included: community uptake, engagement of PCPs, laboratory testing and logistics, and the need for continued outreach to participants who tested negative but may require further testing or enhanced screening (only 4% had done at time of first follow up)

In the meantime, what is safe, inexpensive, and can achieve population testing? Peri-diagnostic testing and cascade diffusion

Yr 1

Yr 2

Yr 3

Yr 4

Yr 5

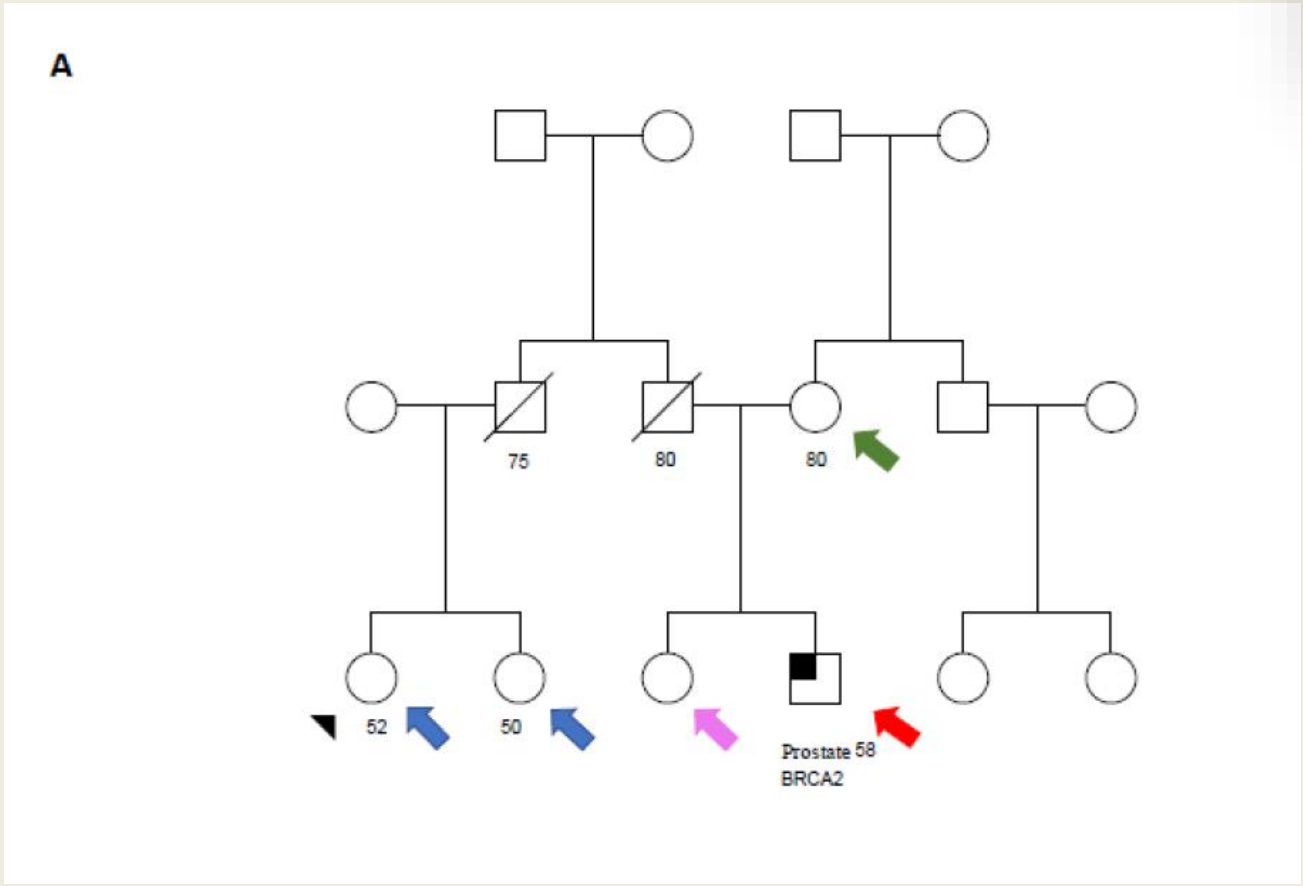
Incident Cancers

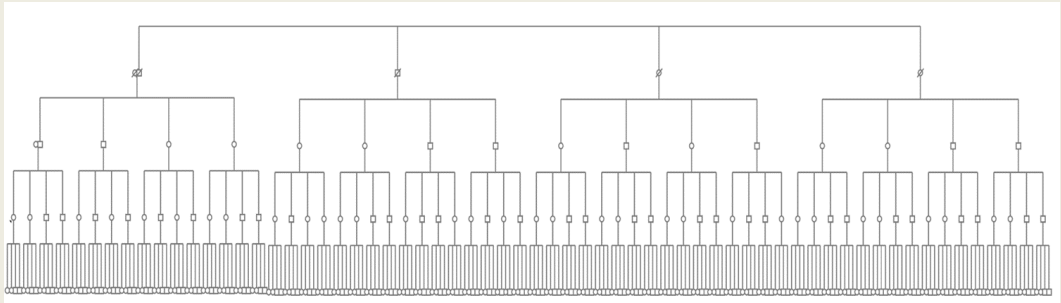
Population test

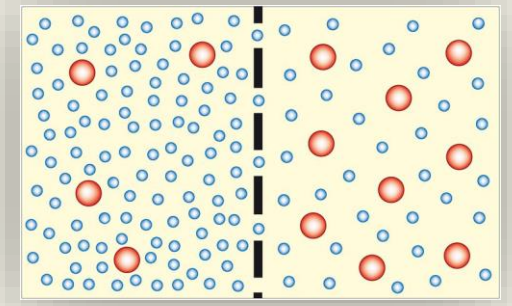
Total Population

Cascade

Cascade Testing







Diffusion

passive

or

facilitated?

How to facilitate?

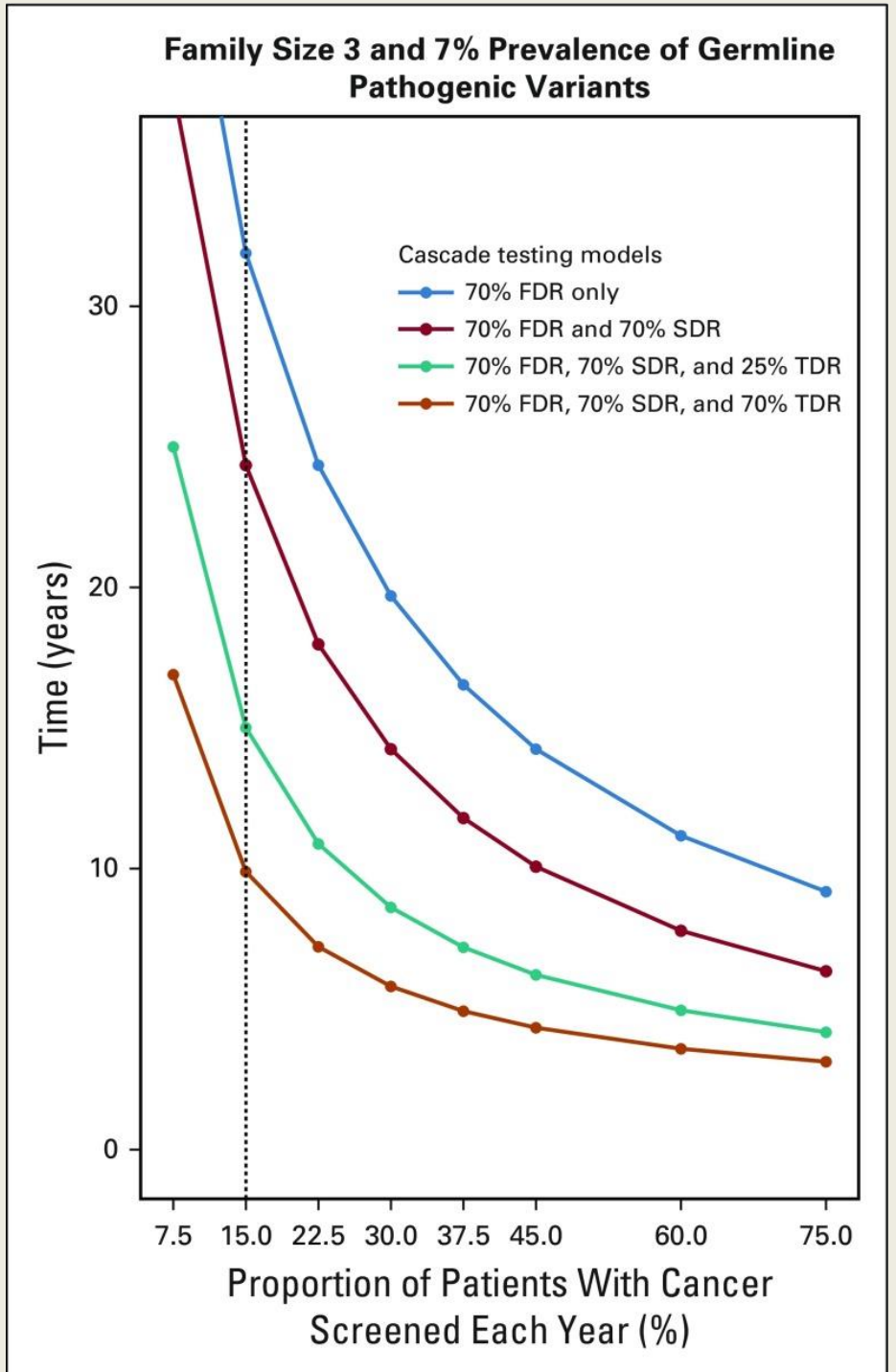
1) Clinician assisted outreach
2) Digital tools

Modeling Cascade testing for Cancer

Time to detect all 3.9 million individuals with pathogenic variants in the United States is 9.9 years.

- **1.7 million cancer cases diagnosed per year in the United States**
- **18 "clinically actionable" genes (utility in cancer prevention or therapeutic targets)**
- **Proportion of incident cases tested 15% (7.5%-75%)**
  [71 NCI-designated cancer centers currently care for 15% pts with cancer, also 1,100 community cancer programs and oncology networks and 250 academic and NCI-designated cancer research centers
- **Proportion of cancer cases tested with germline mutations ranged from 7% (5% to 15%)**

Assuming, 70% Cascade Testing; 7% Prevalence of Germline Mutations, 15% Cases Tested; Family Size of 3:

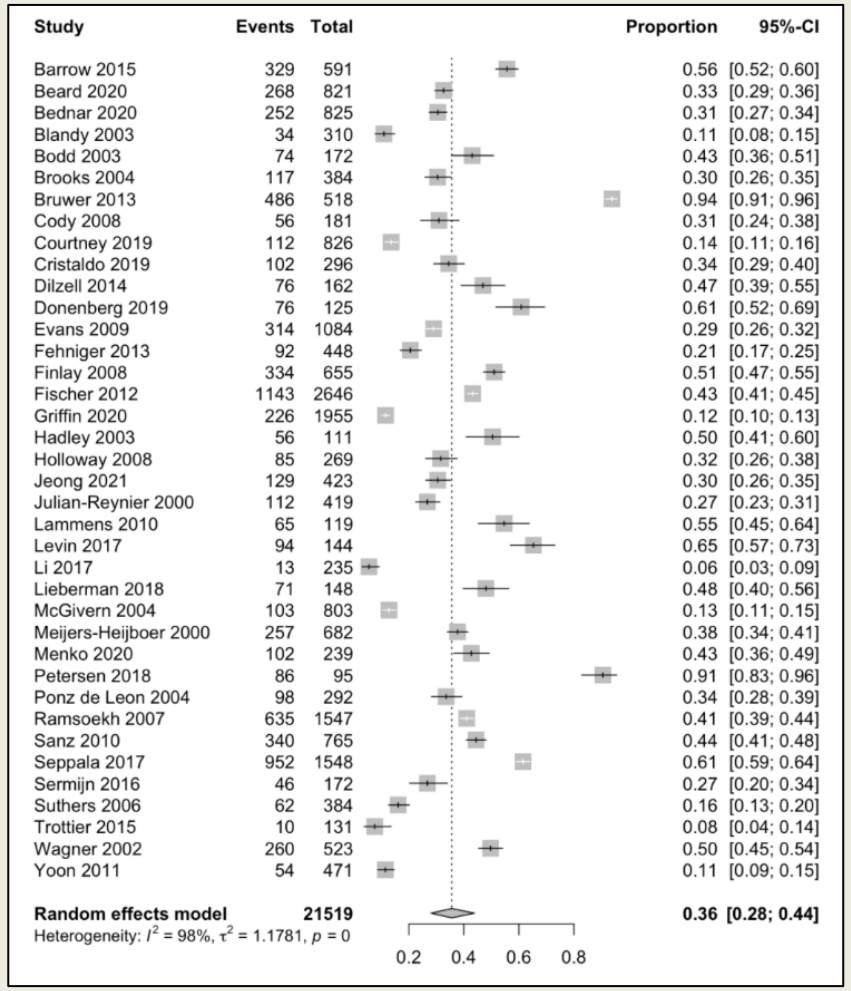


Offit K et al. **J Clin Oncol**. 2020 1;38(13):1398-1408 PMID: 31922925;

Cascade genetic testing for hereditary cancer syndromes
Systematic review and meta-analysis

36% cascade testing

Proband-mediated relative contact



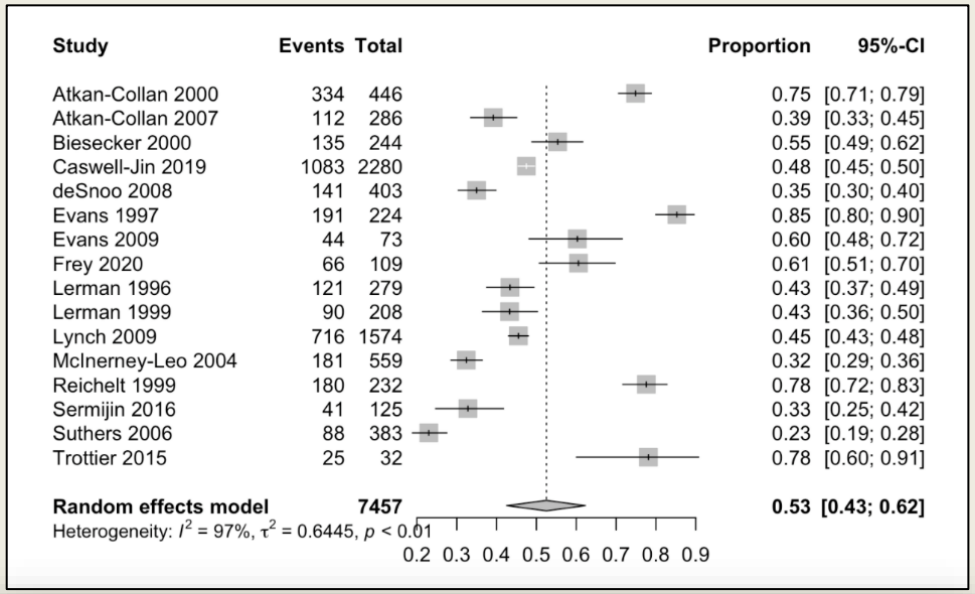
Study	Events	Total	Proportion	95%-CI
Barrow 2015	329	591	0.56	[0.52; 0.60]
Beard 2020	268	821	0.33	[0.29; 0.36]
Bednar 2020	252	825	0.31	[0.27; 0.34]
Blandy 2003	34	310	0.11	[0.08; 0.15]
Bodd 2003	74	172	0.43	[0.36; 0.51]
Brooks 2004	117	384	0.30	[0.26; 0.35]
Bruwer 2013	486	518	0.94	[0.91; 0.96]
Cody 2008	56	181	0.31	[0.24; 0.38]
Courtney 2019	112	826	0.14	[0.11; 0.16]
Cristaldo 2019	102	296	0.34	[0.29; 0.40]
Dilzell 2014	76	162	0.47	[0.39; 0.55]
Donenberg 2019	76	125	0.61	[0.52; 0.69]
Evans 2009	314	1084	0.29	[0.26; 0.32]
Fehniger 2013	92	448	0.21	[0.17; 0.25]
Finlay 2008	334	655	0.51	[0.47; 0.55]
Fischer 2012	1143	2646	0.43	[0.41; 0.45]
Griffin 2020	226	1955	0.12	[0.10; 0.13]
Hadley 2003	56	111	0.50	[0.41; 0.60]
Holloway 2008	85	269	0.32	[0.26; 0.38]
Jeong 2021	129	423	0.30	[0.26; 0.35]
Julian-Reynier 2000	112	419	0.27	[0.23; 0.31]
Lammens 2010	65	119	0.55	[0.45; 0.64]
Levin 2017	94	144	0.65	[0.57; 0.73]
Li 2017	13	235	0.06	[0.03; 0.09]
Lieberman 2018	71	148	0.48	[0.40; 0.56]
McGivern 2004	103	803	0.13	[0.11; 0.15]
Meijers-Heijboer 2000	257	682	0.38	[0.34; 0.41]
Menko 2020	102	239	0.43	[0.36; 0.49]
Petersen 2018	86	95	0.91	[0.83; 0.96]
Ponz de Leon 2004	98	292	0.34	[0.28; 0.39]
Ramsoekh 2007	635	1547	0.41	[0.39; 0.44]
Sanz 2010	340	765	0.44	[0.41; 0.48]
Seppala 2017	952	1548	0.61	[0.59; 0.64]
Sermijn 2016	46	172	0.27	[0.20; 0.34]
Suthers 2006	62	384	0.16	[0.13; 0.20]
Trottier 2015	10	131	0.08	[0.04; 0.14]
Wagner 2002	260	523	0.50	[0.45; 0.54]
Yoon 2011	54	471	0.11	[0.09; 0.15]
Random effects model		**21519**	**0.36**	**[0.28; 0.44]**

Heterogeneity: I^2 = 98%, τ^2 = 1.1781, p = 0

0.2 0.4 0.6 0.8

53% cascade testing

Clinician-mediated direct relative contact



Study	Events	Total	Proportion	95%-CI
Atkan-Collan 2000	334	446	0.75	[0.71; 0.79]
Atkan-Collan 2007	112	286	0.39	[0.33; 0.45]
Biesecker 2000	135	244	0.55	[0.49; 0.62]
Caswell-Jin 2019	1083	2280	0.48	[0.45; 0.50]
deSnoo 2008	141	403	0.35	[0.30; 0.40]
Evans 1997	191	224	0.85	[0.80; 0.90]
Evans 2009	44	73	0.60	[0.48; 0.72]
Frey 2020	66	109	0.61	[0.51; 0.70]
Lerman 1996	121	279	0.43	[0.37; 0.49]
Lerman 1999	90	208	0.43	[0.36; 0.50]
Lynch 2009	716	1574	0.45	[0.43; 0.48]
McInerney-Leo 2004	181	559	0.32	[0.29; 0.36]
Reichelt 1999	180	232	0.78	[0.72; 0.83]
Sermijn 2016	41	125	0.33	[0.25; 0.42]
Suthers 2006	88	383	0.23	[0.19; 0.28]
Trottier 2015	25	32	0.78	[0.60; 0.91]
Random effects model		**7457**	**0.53**	**[0.43; 0.62]**

Heterogeneity: I^2 = 97%, τ^2 = 0.6445, p < 0.01

0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

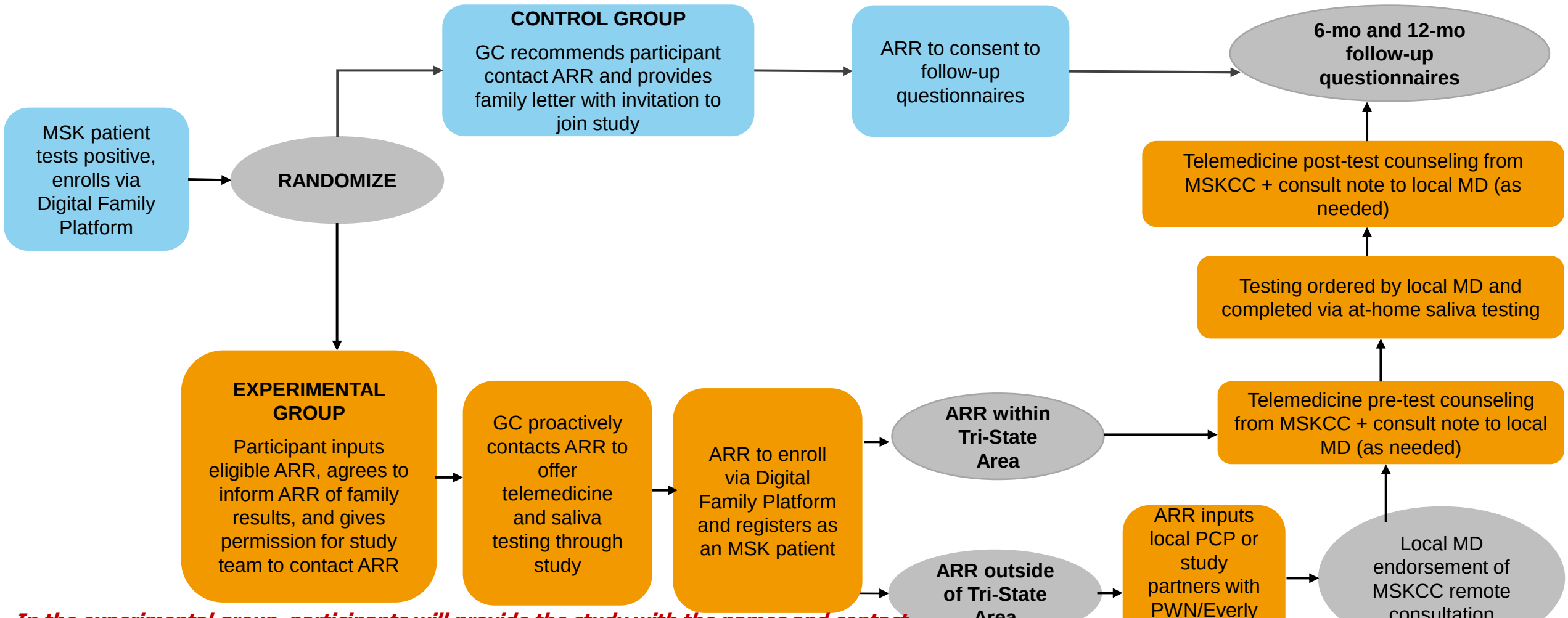
Prospective Feasibility Trial of a Novel Strategy of Facilitated Cascade Genetic Testing Using Telephone Counseling >60% cascade

Melissa K. Frey, MD[1]; Ryan M. Kahn, MD[1]; Eloise Chapman-Davis, MD[1]; Francesca Tubito, MS[1]; Maira Pires, PhD, MS[1]; Paul Christos, MPH, MS[1]; Samantha Anderson, MS[1]; Semanti Mukherjee, PhD[2]; Bailey Jordan, BS[1]; Stephanie V. Blank, MD[3]; Thomas A. Caputo, MD[1]; Ravi N. Sharaf, MD, MS[1]; Kenneth Offit, MD, MPH[2]; Kevin Holcomb, MD[1]; and Steven Lipkin, MD, PhD[1]

Frey...Offit.. et al *JCO in press* 2022

And over a dozen studies in the U.S. exploring cascade approaches.....

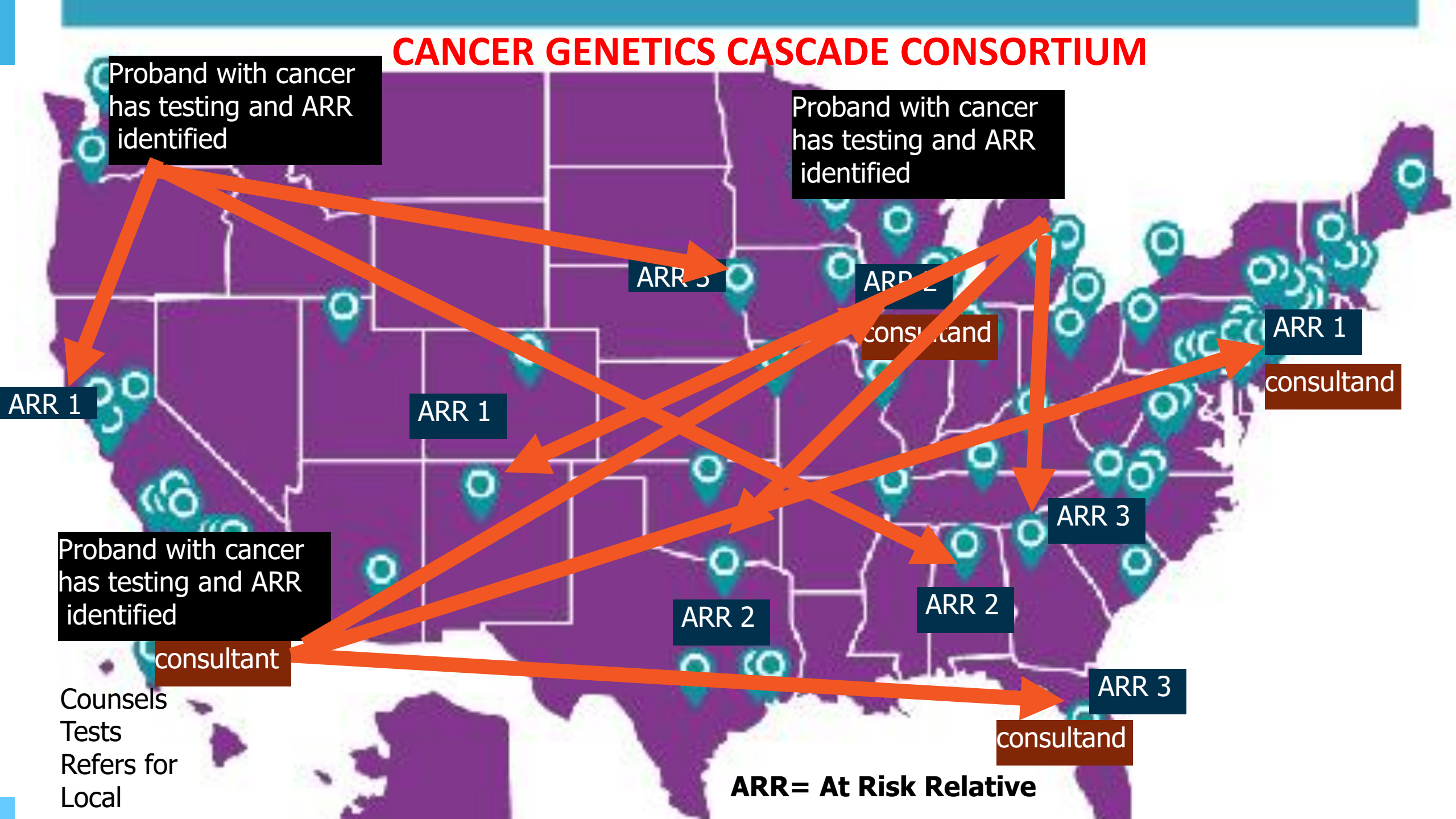
The Effective Familial OutReach via Tele-genetics (EfFORT) Study



In the experimental group, participants will provide the study with the names and contact information of their ARR and agree to notify their relatives of the familial results by a certain date, after which the study team has permission to contact the ARR directly. The proband can change their mind and opt-out of or delay study team member contact of their ARR at any point

Unpublished not for distribution

CANCER GENETICS CASCADE CONSORTIUM



CANCER GENETICS CASCADE CONSORTIUM

•Research and clinical consortium

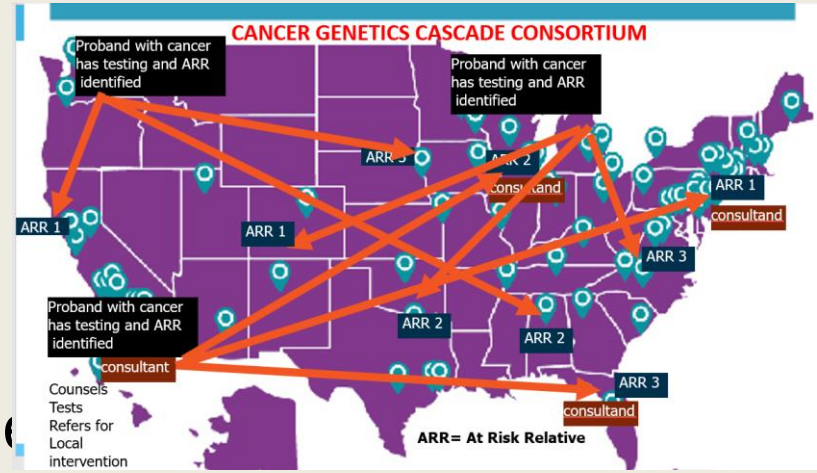
• Members agree that for family members of probands seen at home institution but residing in catchment of Consortium member, a remote consultation model will be used wherein the institution of residence of the proband provides (and bills for) consulting service for ARR via remote model, with the Consortium member in the catchment where the ARR resides serving as the M.D. requestion consultation.

•The local M.D. requesting consultation then becomes the physician of record, and resources of that institution become available for follow up screening, surgery etc

•Consortium follows uniform practices

•Consortium for implementation science/psychosocial research and grants

•Intent to form a consortium as first step



Conclusions

New Approaches and Challenges to Genetic Testing for Cancer Risk

- **Challenges to expansion of clinical based genetic testing include plateau of demand, access, reimbursement, as well as proliferation of consumer-initiated testing for profit companies**
- **Wide dissemination of consumer initiated testing is increasingly encountered and poses risks of analytic, interpretative error, poor communication, cost, access, Role of FDA could/should be enhanced in oversight of Laboratory Developed Tests, including Consumer Initiated Tests as well as Third Party Interpretative Services. The VALID Act is one such mechanism.**
- **New solutions include regulatory empowerment of the FDA via the VALID Act, and role of FTC**
- **New solutions to increase access, decrease complexity include founder mutation screening with internet/digital tools, but challenges in implementation, uptake, health professional willingness /ability to provide follow up, and completion of testing**
- **Cascade testing offers opportunities to scale and facilitate familial diffusion of genomic risk information using web- based approaches and novel remote consultation models that could be national (international) in scope**

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BFOR Study Team: Morgan KM, Hamilton JG, Symecko H, Kamara D, Jenkins C, Lester J, Spielman K, Pace LE, Gabriel C, Levin JD, Tejada PR, Braswell A, Marcell V, Wildman T, Devolder B, Baum RC, Block JN, Fesko Y, Boehler K, Howell V, Heitler J, Robson ME, Nathanson KL, Tung N, Karlan BY, Domchek SM, Garber JE, Offit K.

The Robert and Kate Niehaus Center for Inherited Cancer Genomics
The Breast Cancer Research Foundation
The Sabin Family Research Foundation
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NCI/NHGRI

Views expressed are those of presenter only and not of any of the organizations listed