1 in 550 Pregnancies

Using 346,790 expanded carrier screens to estimate the risk of Mendelian conditions

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Conflicts of Interest

Former employee of Counsyl, a laboratory offering expanded carrier screening.

Current employee of Freenome, a company not currently offering any products whatsoever.

JAMA | Original Investigation

Modeled Fetal Risk of Genetic Diseases Identified by Expanded Carrier Screening

Imran S. Haque, PhD; Gabriel A. Lazarin, MS; H. Peter Kang, MD; Eric A. Evans, PhD; James D. Goldberg, MD; Ronald Wapner, MD

JAMA. 2016; 316(7):734-742

Data available at zenodo.org/record/59628

Outline

1. **Methods**: what's the right way to quantitatively evaluate the merit of a screening protocol from population data?

2. **Results**: what do you find when 1/1000 people in the USA submit to an expanded carrier screen?

3. **Implications**: how do we move the standard of care forward based on this new data?

The **methods** to evaluate large panel tests on a large population.

Background

- **Carrier screening:** testing *prospective parents* for carrier status in recessive conditions that they may pass to their children
- First CF carrier screening guideline issued in 2001; many guideline revisions in intervening 15 years

Table 1. Composition of Racial/Ethnic-Specific Screening Panels Recommended by the American Congress of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG)

	ACOG-Recommended Screening Panel		ACMG-Recommended Screening Panel	
Self-reported Racial/Ethnic Category	Disease Name	Gene Name	Disease Name	Gene Name
African or African American, Southeast Asian, Southern European	Cystic fibrosis	*CFTR*	Cystic fibrosis	*CFTR*
	Hemoglobinopathies	*HBA1/2*, *HBB*	Spinal muscular atrophy	*SMN1*
Ashkenazi Jewish	Cystic fibrosis	*CFTR*	Cystic fibrosis	*CFTR*
	Canavan disease	*ASPA*	Spinal muscular atrophy	*SMN1*
	Familial dysautonomia	*IKBKAP*	Bloom syndrome	*BLM*
	Tay-Sachs disease	*HEXA*	Canavan disease	*ASPA*
			Familial dysautonomia	*IKBKAP*
			Fanconi anemia type C	*FANCC*
			Gaucher disease	*GBA*
			Mucolipidosis IV	*MCOLN1*
			Niemann-Pick disease type A	*SMPD1*
			Tay-Sachs disease	*HEXA*
Cajun or French Canadian	Cystic fibrosis	*CFTR*	Cystic fibrosis	*CFTR*
	Tay-Sachs disease	*HEXA*	Spinal muscular atrophy	*SMN1*
East Asian, Finnish, Hispanic, Middle Eastern, mixed or other Caucasian, Native American, Northern European, Pacific Islander, South Asian, unknown	Cystic fibrosis	*CFTR*	Cystic fibrosis	*CFTR*
			Spinal muscular atrophy	*SMN1*

Background

- **Carrier screening:** testing *prospective parents* for carrier status in recessive conditions that they may pass to their children
- First CF carrier screening guideline issued in 2001; many guideline revisions in intervening 15 years
- **Expanded carrier screening:** carrier screening for 10s-100s of conditions, beyond society guidelines

To what extent are guidelines predictive/comprehensive of the risk of recessive conditions?

Methodology Considerations

Which data to sum up?	Which individuals?
	Which diseases?
	Which mutations/variants?
How to run the summation?	Metrics for panel evaluation

Which individuals and diseases?

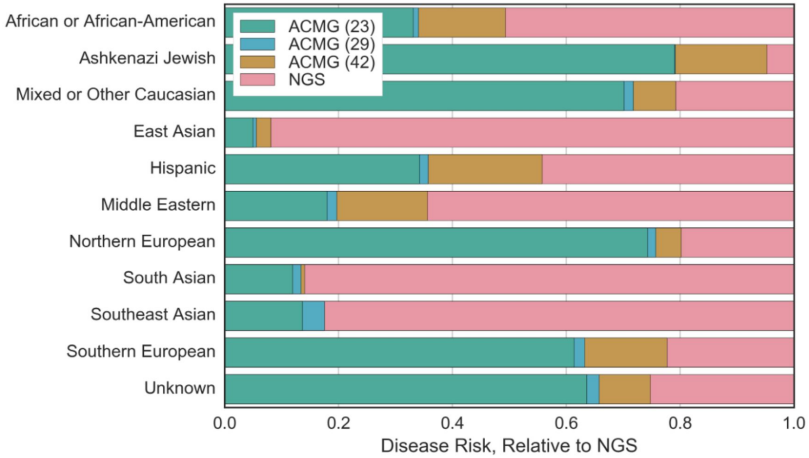
- **Remove obvious sources of sample bias:** Excluded any individuals with indications other than “routine carrier testing”: infertility, known FHx, known carriers, donor screening, “other”.

- **Only consider conditions of clinical relevance**: Included only conditions ranked as “profound” (like Canavan) or “severe” (like CF). Specifically excluded A1AD, familial Mediterranean fever.

Which variants/mutations?

- Important to incorporate NGS data with broad exonic coverage to properly treat non-European populations.

- Follow ACMG criteria (or more conservative) for classification; exclude VUS.



Beauchamp KA et al. NSGC 2016

What is an appropriate metric to compare panels?

Carrier frequency: *Probability that a random individual carries at least one pathogenic allele in at least one condition on a panel.*

Pros	• Conceptually simple, esp. for single genes or small panels
Cons	• AR conds require *both* parents to be carriers for elevated risk. • Can't fairly compare AR and XR conds. • In the limit, everyone is a carrier.

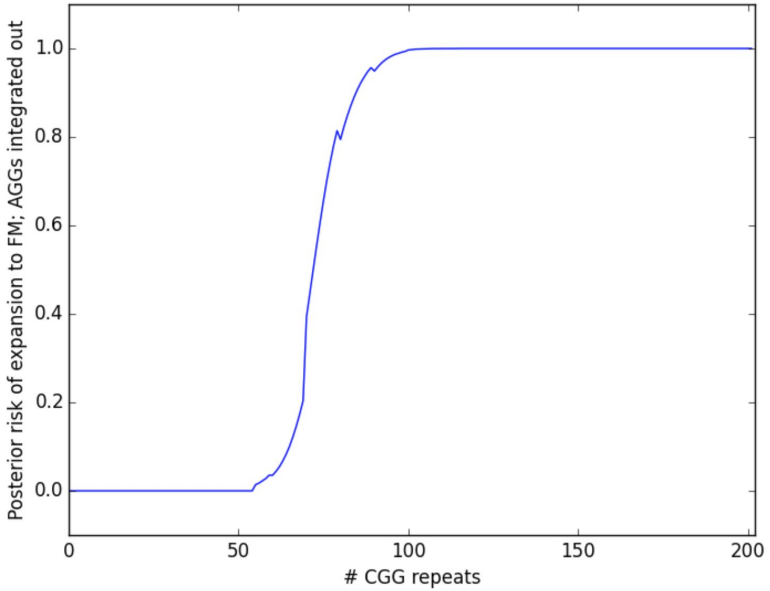
What is an appropriate metric to compare panels?

Carrier couple frequency/at-risk couple rate: *Probability that, for at least one condition on a panel, both individuals in a random mating pair carry at least one pathogenic allele in the same autosomal recessive condition OR the female carries at least one pathogenic allele for an X-linked condition.*

Pros	• Properly stratifies elevated risk for “simple” AR and XR conds.
Cons	• Some important conditions are more complicated than the “simple” model.

Complex Inheritance: Fragile X (*FMR1*)

X-linked 5’UTR CGG repeat that expands on maternal transmission.



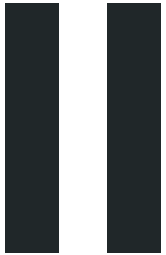
55 vs 155 repeat mothers are “carrier couples” with different risk.

What is an appropriate metric to compare panels?

(Modeled fetal) disease risk: *Probability for a random mating pair that a random zygote will be hom/compound het for pathogenic alleles in at least one condition from a panel.*

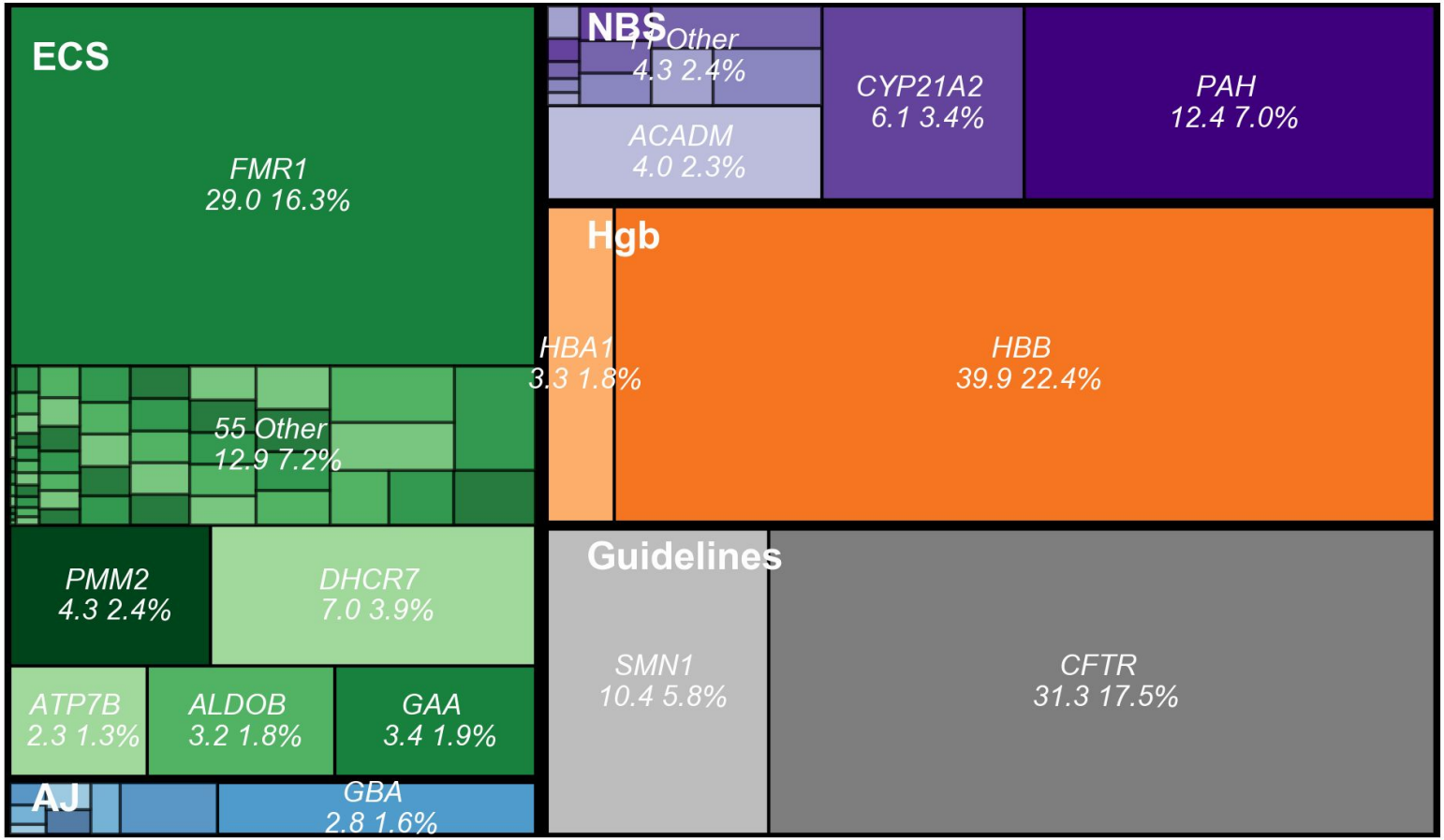
Pros	• Closer to the metric we care about: risk in the next generation
Cons	• Complicated to compute • Doesn't incorporate fetal viability or variable penetrance

This metric can fairly evaluate conditions with complex inheritance.

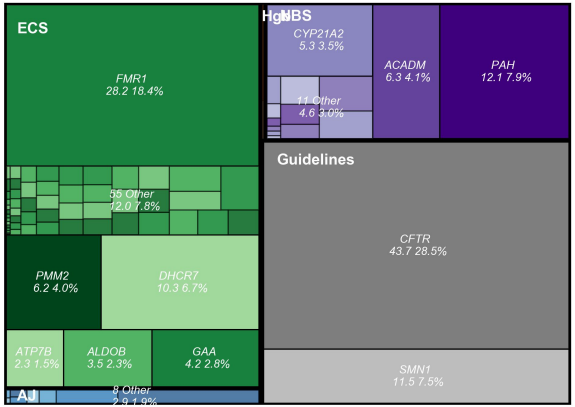


The **results** of evaluating the disease risk of 94 conditions in 346,790 individuals from the USA

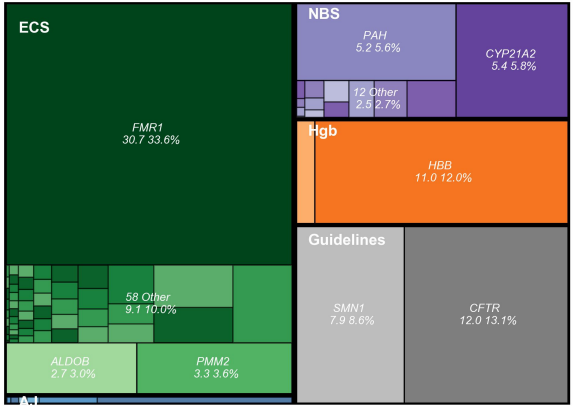
Overall risk: ~1/550 pregnancies in the USA



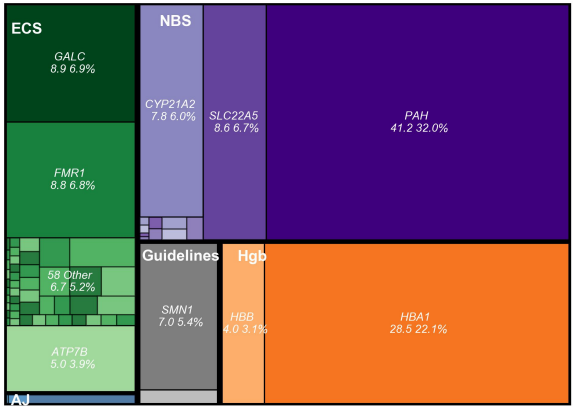
Case Studies



Northern European

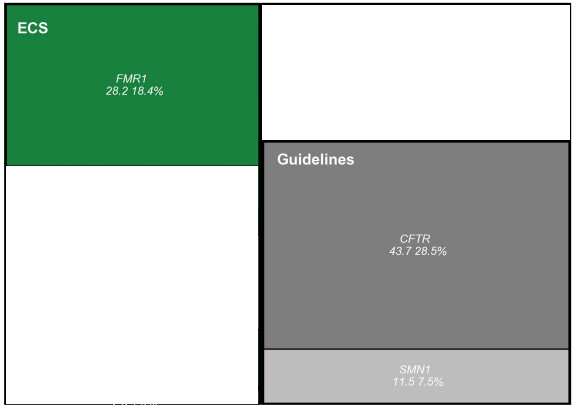


Hispanic



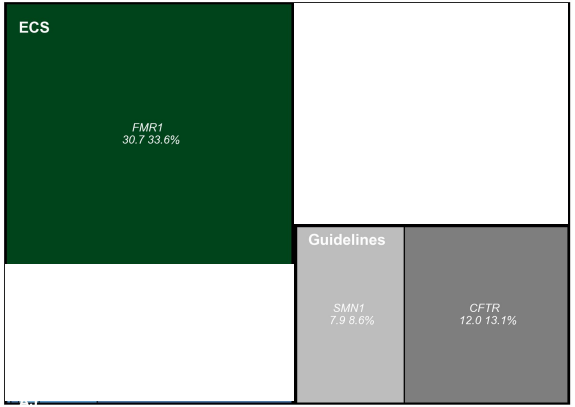
East Asian

Single-gene Screening: CF, SMA, Fragile X



Northern European

CF > FX > SMA



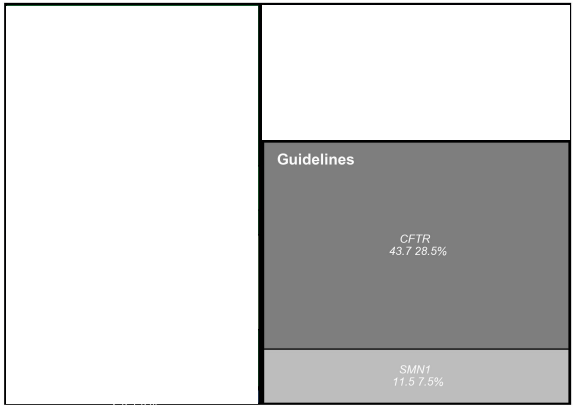
Hispanic

FX > CF ~ SMA

East Asian

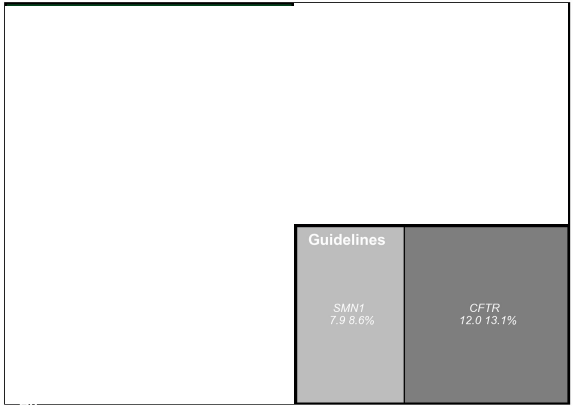
FX ~ SMA >> CF

ACOG/ACMG guidelines



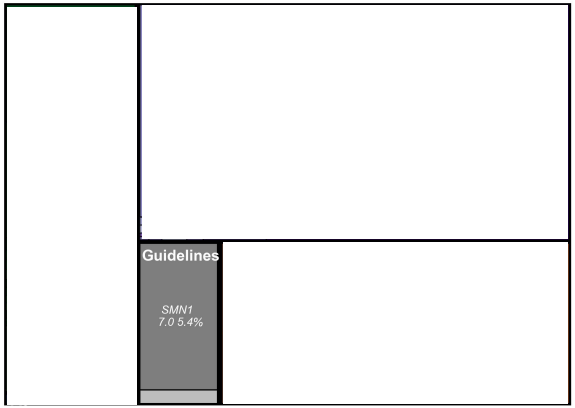
Northern European

CF > SMA > FX
35% of risk w/i guidelines



Hispanic

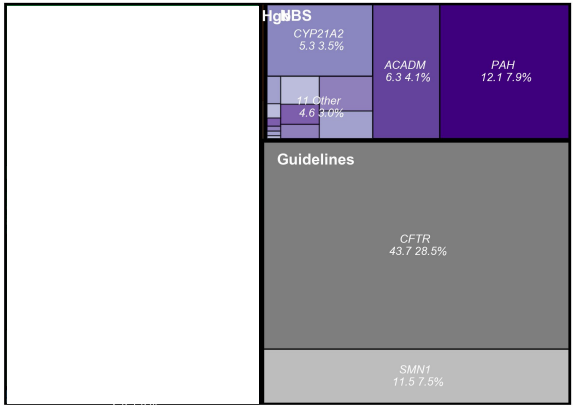
FX > CF ~ SMA
21% of risk w/i guidelines



East Asian

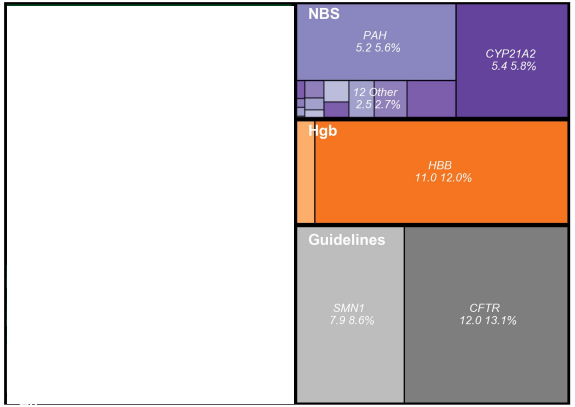
FX ~ SMA >> CF
6% of risk w/i guidelines

ACOG/ACMG guidelines + NBS



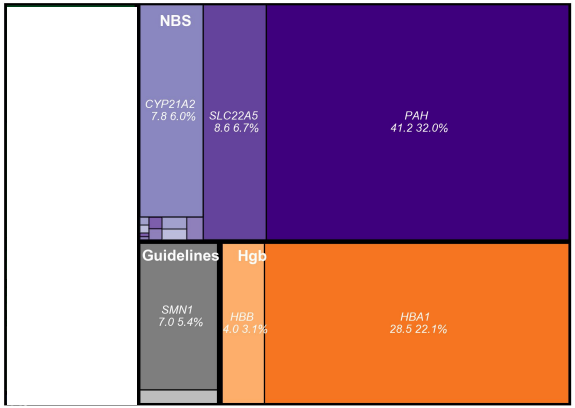
Northern European

CF > SMA > FX
35% of risk w/i guidelines
53% of risk w/CS+NBS



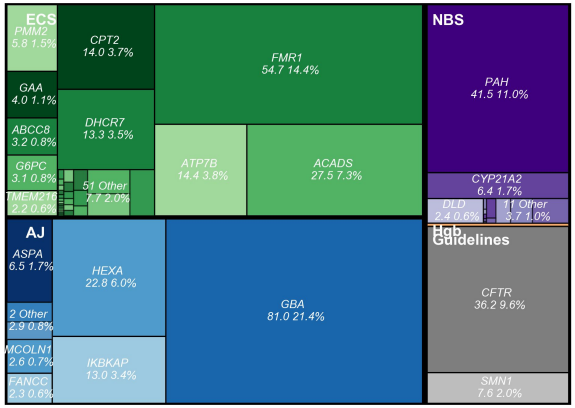
Hispanic

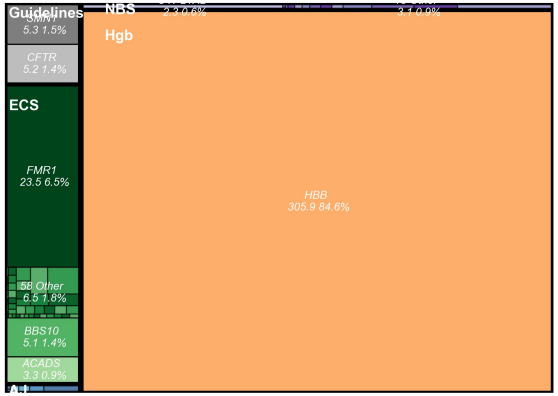
FX > CF ~ SMA
21% of risk w/i guidelines
47% of risk w/i CS+NBS

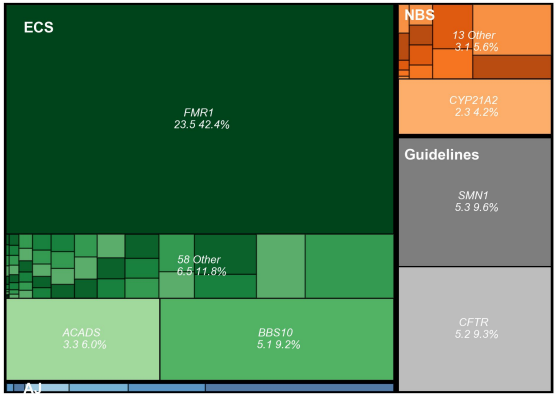


East Asian

FX ~ SMA >> CF
6% of risk w/i guidelines
76% of risk w/i CS+NBS







Ashkenazi Jewish

FX > CF > SMA
45% of risk w/i guidelines
58% of risk w/CS+NBS

African-American

SCD >>> FX >> CF = SMA
87% of risk w/i guidelines
89% of risk w/i CS+NBS

African-American (ex *HBB*)

FX >> CF = SMA
18% of risk w/i guidelines
28% of risk w/i CS+NBS

Results: Summary

- Privileged position of CF/SMA is unjustified outside of European population.
- Fragile X is more common than current single-gene recommendations, even accounting for incomplete transmission.
- Newborn screening is not an adequate substitute for ECS
    - Large burden of monogenic disease that is included in neither CS nor NBS recommendations
    - Many conditions caught by NBS could be detected earlier for reproductive autonomy.

The **future work** of integrating population data into population care: getting past two red herrings.

Sequencing-based expanded carrier screening will definitely lead to false positive results

(from laboratory error, interpretive error, reporting error, etc).

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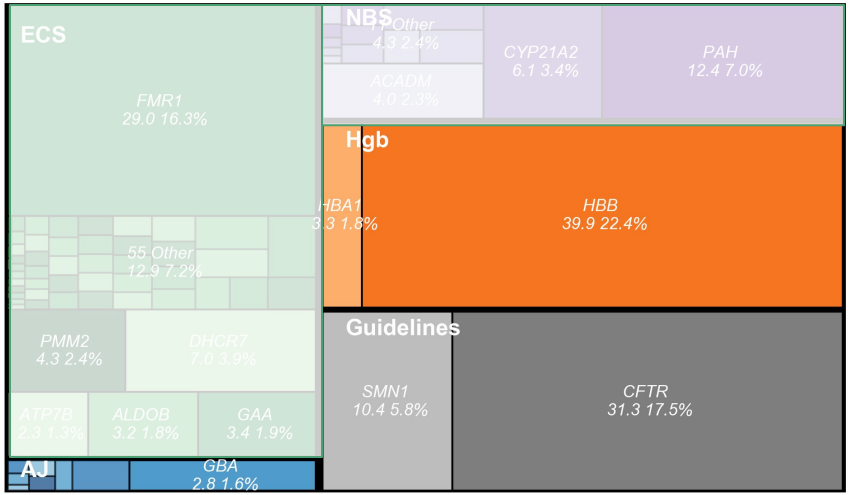
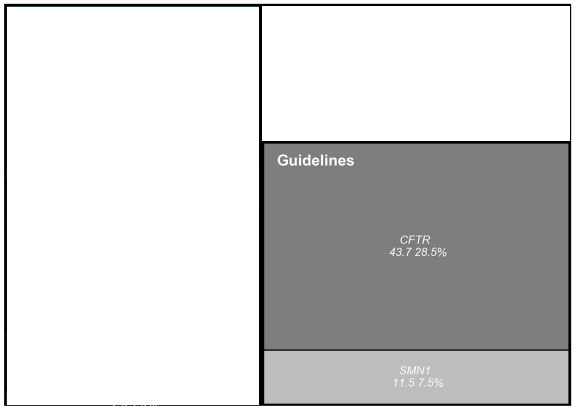
But there's a lot to which we are willfully blinding ourselves:



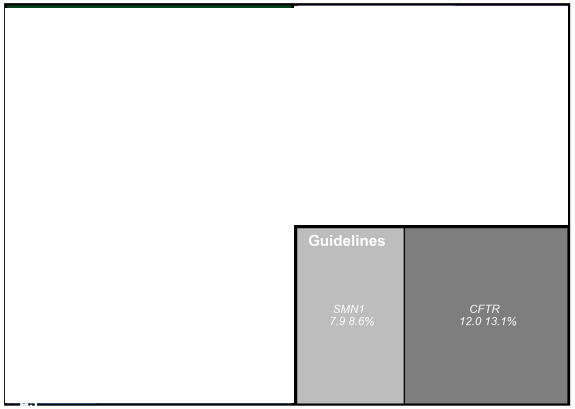
False positives vs false negatives

Failing to perform expanded carrier screening will also certainly generate a substantial number of false *negatives*.

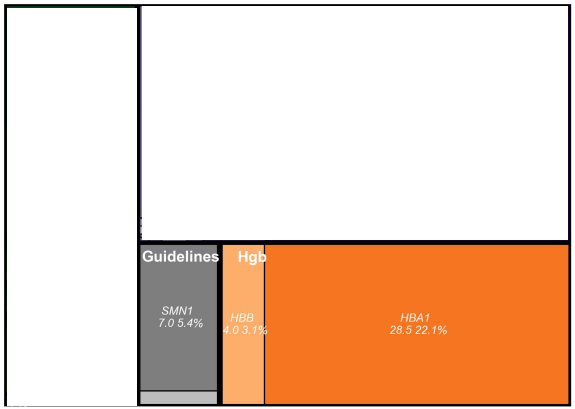
These false negatives are likely to be distributed in an ethnically/racially inequitable fashion.



Northern European



Hispanic



East Asian

PROSPECTIVE RANDOMIZED CONTROLLED TRIALS ARE THE ONLY WAY TO MAKE DECISIONS...

Research Original Investigation

Severe Genetic Disease Risk Identified by Expanded Carrier Screening

Conclusions

In a population of diverse races and ethnicities, expanded carrier screening may increase the detection of carrier status for a variety of potentially serious genetic conditions compared with current recommendations from professional societies. Prospective studies comparing current standard-of-care carrier screening with expanded carrier screening in at-risk populations are warranted before expanded screening is adopted.

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Conclusions

In a population of diverse races and ethnicities, expanded carrier screening may increase the detection of carrier status for a variety of potentially serious genetic conditions compared with current recommendations from professional societies. Prospective studies comparing current standard-of-care carrier screening with expanded carrier screening in at-risk populations are warranted before expanded screening is adopted.

RIGHT?

Autosomal + Recessive = Problem

Quadratic falloff of frequency for autosomal affecteds poses a big problem for enrolling “unselected prospective” studies. How many individuals need to enter the top of the funnel to study the following?

Condition	**Carrier frequency**	**Carrier-couple frequency**	**Affected frequency**	**Study size (init. enroll.)**
CFTR (any)	1 / 25	1 / 625	1 / 2500	25,000
CFTR (F508del)	1 / 40	1 / 1600	1 / 6400	64,000
GALC (any)	1 / 230	1 / 53000	1 / 212000	2.1M

Unselected prospective trials: not feasible for most genetic conditions or variants.

Limitations of the RCT design in genetics

The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer

A Report of the Association for Molecular Pathology

"**Limiting medical care to what has been validated by RCTs is neither practical nor appropriate**... retrospective studies are more suitable for determining if mutations in a particular gene are correlated with a specific clinical presentation.

Given these limitations, **alternate types of well-designed prospective and retrospective clinical study designs...should be recognized as appropriate and sufficient for determining [clinical utility] for molecular diagnostics"**

Joseph L *et al.*, J Mol Diagn, 18(5) Sep 2016, 605-619

IV

Conclusions

Conclusions

1. **Methods matter**: to draw population conclusions, sequence large populations for relevant conditions, exclude obvious sources of bias, and weight by risk to next generation to handle variable transmission.

2. **There is a significant burden of Mendelian disease that goes unrecognized by current screening guidelines**, and the consequences of those guidelines are not realized in an equitable way.

3. **Evaluation methods must become more sophisticated:** criteria and study designs applied in earlier medical genetics are numerically infeasible for today's frontier. "If you choose not to decide, you still have made a choice."

Acknowledgments

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Ron Wapner (Columbia)

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Questions?

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JAMA paper data: zenodo.org/record/59628