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Preconception to Prenatal Genetic Testing

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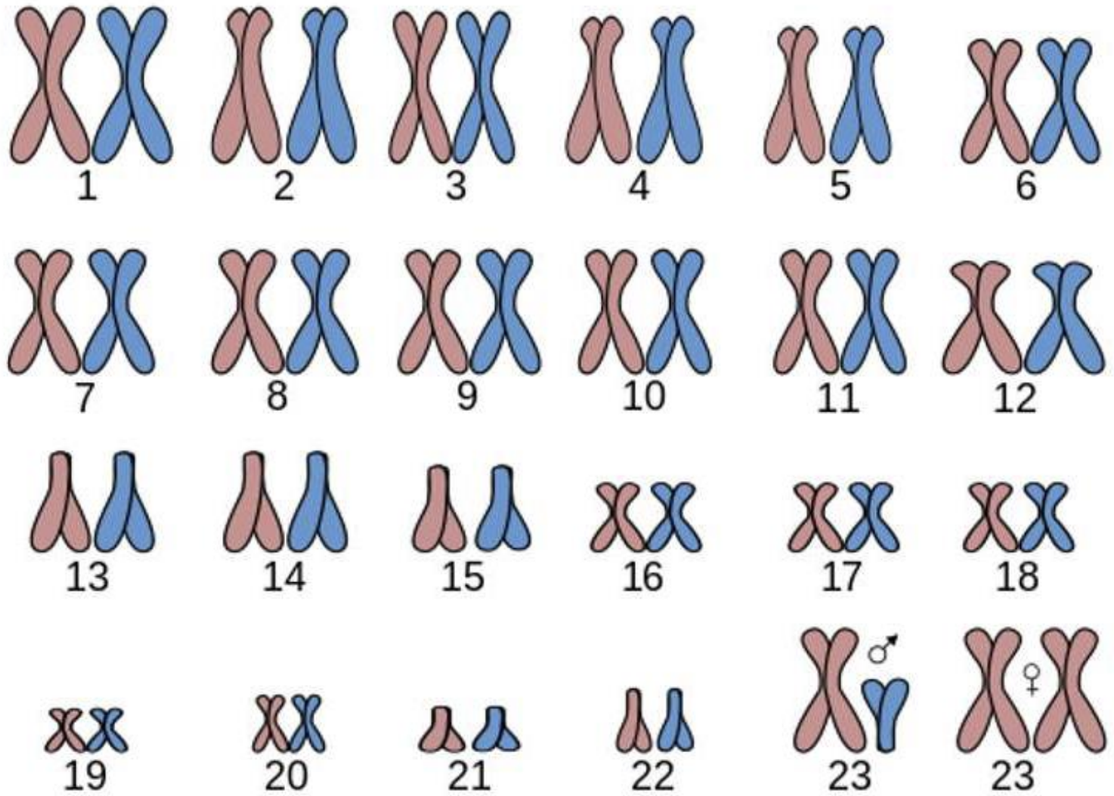
make history.

Declaration

I am not a clinical geneticist or genetic counsellor

Genetics



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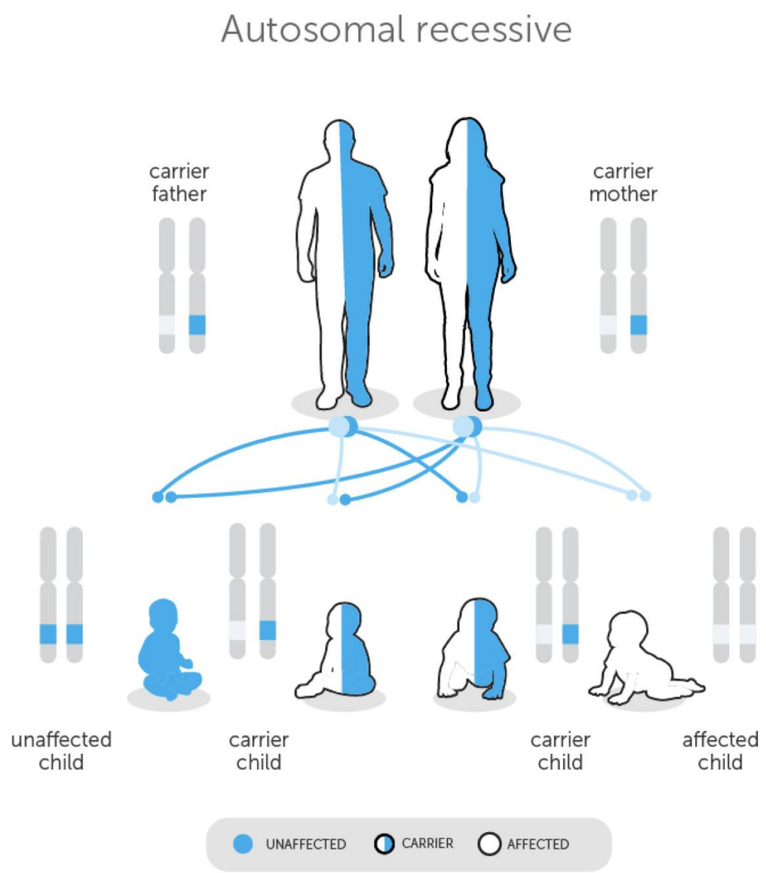
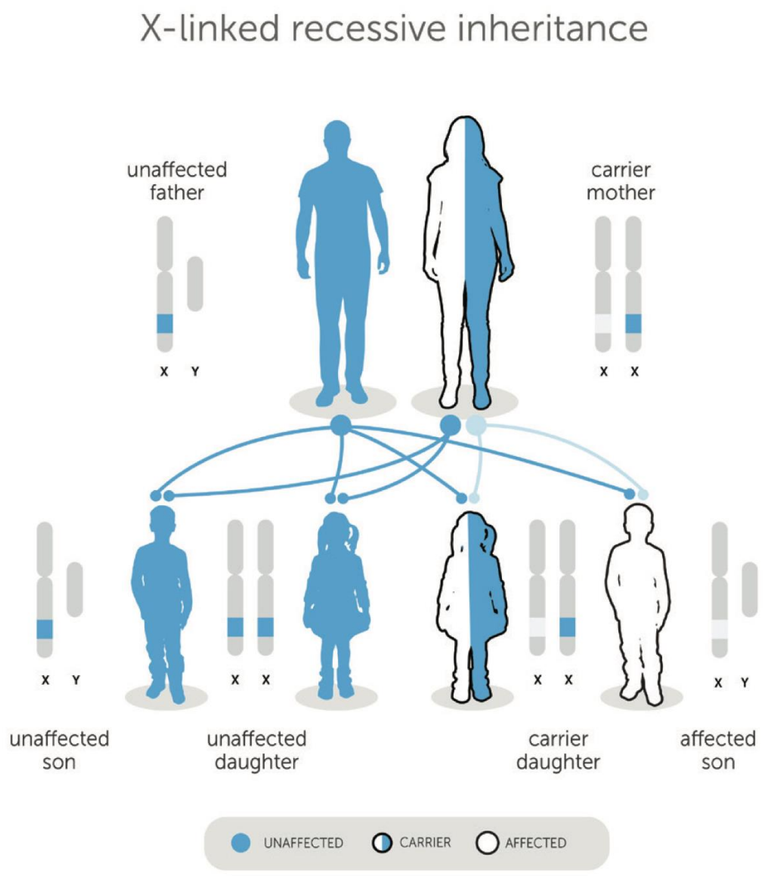
Patterns of inheritance





How things have changed

1970's - carrier screening programs introduced; based on ethnicity –Ashkenazi Jewish community; Mediterranean populations

1989 - CFTR gene identified

1990's - "CF screening should be offered to all individuals or couples seeking prenatal or preconception care"

2000's - human genome sequenced; screening for small panels of conditions possible

2010 - expanded carrier screening available

2020's - Implementation of population-wide expanded carrier screening

2023, November - MBS item number for 3-condition carrier screening

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What is genetic carrier screening?

Genetic test

Provides a person or couple with information about their chance of having a child with an inherited genetic condition

- Identifies whether someone is a carrier for a range of inherited genetic conditions
- These do not generally affect the individual's own health
- Carrier status is relevant to family planning

How common is it?

3-condition screening:

- **88% of carriers have no family history**
- **1 in 20 individuals is a carrier**
- **1 in 240 couples increased chance of affected infant**

Large panel/expanded screening:

- **2% of couples have an increased chance of an affected infant**

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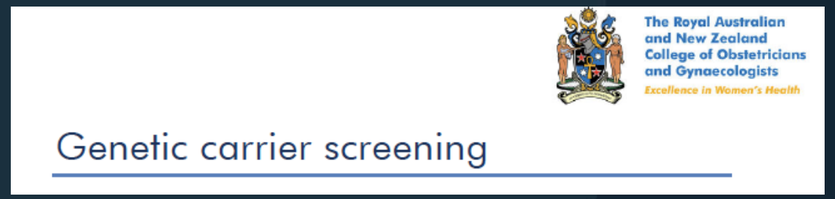
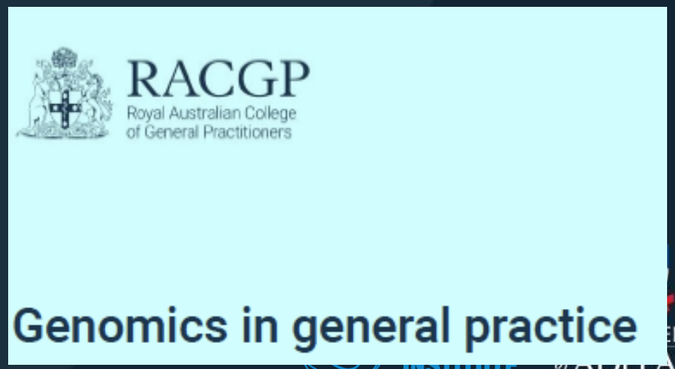
“Information on carrier screening for carrier genetic conditions should be offered to all women planning a pregnancy or in the first trimester of pregnancy. Options for carrier screening include screening with a panel for a limited selection of the most frequent conditions (CF, SMA, FXS) or screening with an expanded panel that contains many disorders (up to hundreds)”

“Information on carrier screening for at least the more common genetic conditions that affect children (CF, SMA, FXS) should be offered to low-risk women and couples regardless of family history and ethnicity. Women/couples can be offered larger panels of genes for carrier screening (expanded carrier screening).”





Options for carrier screening

Small panel screening

- 3 most common inherited conditions (CF, SMA, FXS)
- Performed sequentially

Large panel/expanded carrier screening

- 100’s of condition
- Variable incidence and severity
- Simultaneous screening generally performed

Small panel screening

Genetic condition	Carrier frequency	Genetics	Carrier detection rate	Phenotype
Cystic fibrosis	1 in 25	CFTR 175 CF-causing variants screened	~95%	Recurrent lung infections, malabsorption, hyperglycemia, shortened life span
Spinal muscular atrophy	1 in 40	SMN1 deletion	~95%	Severe/variable muscle weakness, possible death in childhood
Fragile x syndrome	1 in 250	FMR1 expansion and AGG interruption analysis	>99%	Intellectual disability, autism, premature ovarian failure, tremor/ataxia

Variation in large panel carrier screening

No.	Provider	Type of provider	Country	No. of genes[a]	List price (original currency)	Price per couple (US$ 2023)[b]	Insurance available	Subset	Sample	Turnaround time[c]	Genotyping or sequencing
1	23andMe	Company	USA	44	US$228 per test	$456	Not reported	Not reported	Saliva	21–28 days	Genotyping
2	Academic medical center Amsterdam	Medical hospital	The Netherlands	50	€650 per test	$1650	Yes	Yes	Blood	56 days	Sequencing
3	Baylor genetics	Company	USA	422	Not reported	Not available	Yes	Yes	Blood/saliva	14 days	Sequencing
4	GenPath diagnostics	Company	USA	179	Not reported	Not available	Yes	Yes	Blood/saliva	Not reported	Combined
5	Igenomix	Company	Spain	2054	US$550 per test	$1100	Not reported	Yes	Blood	28 days	Sequencing
6	Integrated genetics	Company	USA	578	US$2160 per test	$4320	Yes	Yes	Blood	14 days	Combined
7	Myriad	Company	USA	177	US$240 per test	$480	Yes	Yes	Blood/saliva	14 days	Combined
8	Natera	Company	USA	422	US$349 per test	$698	Yes	Yes	Blood	14–21 days	Sequencing
9	CentoGene	Company	Germany	330	€1000 per test €1895 per couple	$2405	Yes	Not reported	Blood	21 days	Sequencing
10	Fulgent	Company	USA	427	US$349 per test US$449 per couple	$449	Yes	Yes	Blood/saliva	14 days	Sequencing
11	Invitae	Company	USA	569	US$250 per test US$350 per couple	$350	Yes	Yes	Saliva	14 days	Sequencing
12	Mastantuoni (2018)	Source unclear	Italy	538	Not reported	Not available	Not reported	Not reported	Not reported	Not reported	Not reported
13	PathWest laboratory medicine	Research team	Australia	474	Not reported	Not available	Not reported	Not reported	Not reported	Not reported	Not reported
14	Sema4	Company	USA	283	US$249 per test; US$349 per couple	$349	Yes	Yes	Blood/saliva	14 days	Combined
15	Virtus genetics	Company	Australia	526	AU$650 per test	$898	Not reported	Yes	Blood	10–15 days	Not reported
16	VCGS	Research team	Australia	1300	AU$2200 per couple	$1520	Not reported	Yes	Saliva	35–42 days	Combined
17	QuestAdvanced	Company	USA	422	US$300 per test	$600	Yes	Yes	Blood	Not reported	Sequencing
18	MGZ medical genetics center	Company	Germany	610	Not reported	Not available	Yes	Yes	Blood	21–42 days	Sequencing
19	EasyDNA	Company	Australia	416	AU$680 per test AU$1300 per couple	$898	Not reported	Not reported	Blood	29–40 days	Sequencing
20	Monash IVF	Company	Australia	400	AU$695 per test AU$1250 per couple	$864	Not reported	Not reported	Saliva	28–42 days	Not reported

(Continues)

An overview of reproductive carrier screening panels for autosomal recessive and/or X-linked conditions: How much do we know?

Tianjiao Wang[1,2] | Paul Scuffham[1,2] | Joshua Byrnes[1,2] | Martin B. Delatycki[3,4] | Martin Downes[1,2]

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Access inequity

Who is requesting testing?

Obstetricians 53%

GPs 20%

When are women testing?

During pregnancy 68%

- GPs 53%
- Obstetricians 89%

Who is testing?

- Majority of women from high SES areas

Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome and spinal muscular atrophy: patterns of community and healthcare provider participation in a Victorian screening program

Ruth Leibowitz[A,*], Sharon Lewis[B,C], Jon Emery[D], John Massie[E,F,G], Melanie Smith[H], Martin Delatycki[H,I,J] and Alison Archibald[J,K,*]

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Results from carrier screening

Low chance

- Very small residual chance of having an affected child

Increased chance

- Genetic counselling required and available
- Specialist referral required particularly for rarer conditions
- Results can be unexpected and alter reproductive plans

Reproductive options

Conceive spontaneously

- Prenatal invasive testing – CVS or amniocentesis
  - Continue or end affected pregnancy
- Test at birth

IVF and preimplantation genetic testing

- Donor (sperm, egg, embryo)
- Adoption

Antenatal invasive diagnostic testing

CVS

- Performed from 11 weeks' gestation

Amniocentesis

- Performed from 15 weeks' gestation

Quoted estimated of fetal loss were 0.5-1.0%

- More recent meta-analysis suggested fetal loss rates in hands of experienced operators do not differ between CVS and amniocentesis and may be as low as 1 in 900

Australian Reproductive Genetic Carrier Screening project (Mackenzie's Mission)

- 10,000 couples recruited across Australia through specific trained healthcare providers
- screening for 1300 genes associated with ~750 inherited genetic conditions
- ~2% of couples received an increased chance result
  - 80% of these increased chance results were not for CF, FXS, or SMA
- Screening for a large panel of genes is more cost effective than 3 condition screening or no screening
- ~80% chose to avoid the condition in their offspring through use of reproductive options
- 96% felt screening should be available to all

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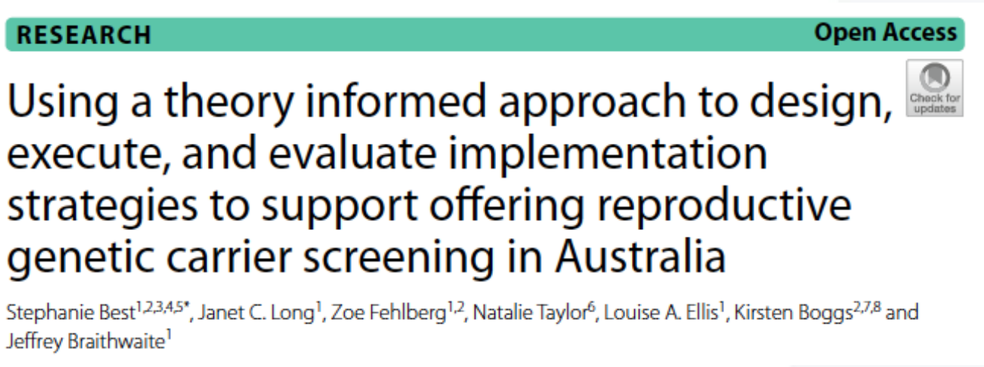
Implementation – challenges and barriers

Identified barriers

- Lack of skills and knowledge
- Lack of practice
- Lack of confidence
- Lack of time



RESEARCH Open Access

Using a theory informed approach to design, execute, and evaluate implementation strategies to support offering reproductive genetic carrier screening in Australia

Stephanie Best[1,2,3,4,5*], Janet C. Long[1], Zoe Fehlberg[1,2], Natalie Taylor[6], Louise A. Ellis[1], Kirsten Boggs[2,7,8] and Jeffrey Braithwaite[1]

Implementation strategies trialled in Mackenzie's Mission

- Skills video (7 minutes) by genetic counsellors to GPs
- Waiting room poster
- Online information and consent

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Implementation

Harnessing available resources

- Print, online
- Genetic counsellors

Where would it be easiest to start having these conversations?

- Preference for prepregnancy c.f. early pregnancy
- Postnatal consultations? 6 week/6 month/12 month vaccination appointments?
- Similar to brief conversations to stop smoking?

Resources

https://www.vcgs.org.au/health-professionals/prepair-carrier-screening/

https://www.vcgs.org.au/api/media/MGF-142-prepair-brochure/

https://www.youtube.com/watch?v=zyE5DyQXctc – VCGS prepair genetic carrier screening video 2:50

https://ranzcog.edu.au/wp-content/uploads/2022/06/Reproductive-carrier-screening.pdf

https://mercyperinatal.com/for-patients-and-families/genetic-testing-prior-to-conceiving

https://www.health.nsw.gov.au/kidsfamilies/MCFhealth/maternity/Pages/reproductive-genetic-carrier-screening.aspx

https://mercyperinatal.com/event/genetics-in-pregnancy-course

Genetics in Pregnancy course. Lisa Hui, Tristan Hardy

- Aneuploidy screening
- Genetic carrier screening
- Prenatal diagnosis
- ART and preimplantation genetic testing

~12 hours elearning at your own pace; 40 CPD points; $385

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Questions?