THE PATHCARE NEWS

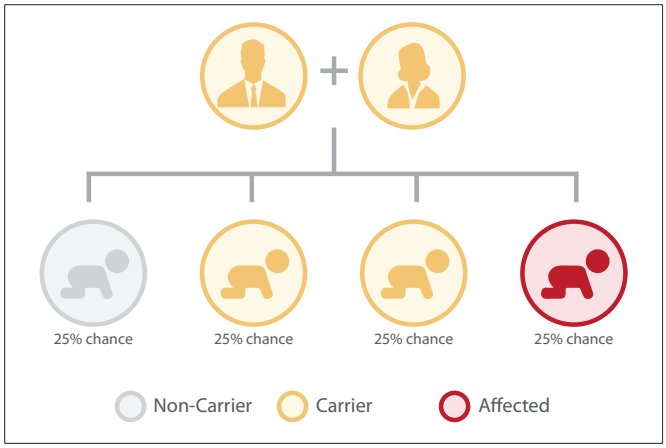
PathCare referrals to Invitae laboratory

Preconception Carrier Screening

PathCare offers a referral service to Invitae Laboratory in the USA. Invitae offers an extensive genetic test menu over a broad range of clinical areas, and has **recently introduced comprehensive carrier screening to their testing catalogue.**

What Is Carrier Screening?

Carrier screening is used to identify carriers of autosomal recessive conditions or female carriers of X-linked recessive disorders. Carriers of autosomal recessive conditions are generally asymptomatic and therefore unaware that they carry a certain condition. If both partners are found to be carriers of the same recessive condition, then they have a 25% (or 1 in 4) chance of having an affected child.



X-linked recessive conditions are caused by mutations in genes on the X chromosome. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. Identifying female carriers can be useful for understanding the risks related to having an affected male child (50% risk).

Knowing one's carrier status allows couples at risk to discuss options such as prenatal diagnosis or preimplantation genetic testing in the context of appropriate genetic counselling.

Compared to Down syndrome, for which screening is routinely offered, single-gene gene disorders as a whole are more common:

- 1 in 100 babies are born with an inherited disease (Compared to 1 in 700 babies born with Down syndrome)[1]
- 20-30% of infant deaths are due to genetic disorders[2]

Who Should Have Carrier Screening?

All patients who are pregnant or considering pregnancy should be informed about genetic carrier screening. Carrier screening identifies patients who are at increased risk of having a child affected with a genetic disorder, providing actionable information for the next steps of their reproductive journey.

Each patient carries approximately 4-6 heterozygous mutations in genes that cause autosomal recessive conditions. **The risk of the patient and her partner being a carrier of a mutation in the same gene is 1-2.5%. However, certain population groups are at increased risk for particular recessive conditions.**

For example: The American College of Medical Genetics (ACMG) recommends screening of **eight conditions in Ashkenazi Jewish couples[3]:**

Bloom syndrome	Gaucher disease
Canavan disease	Mucolipodosis type IV
Familial dysautonomia	Niemann-Pick disease type A/B
Fanconi anaemia group C	Tay Sachs disease

[1] WHO – Genes and Human Disease: Monogenic diseases. http://www.who.int/genomics/public/geneticdiseases/en/index2.html

[2] Berry RJ, Buehler JW, Strauss LT, et al. 1987. Birth weight-specific infant mortality due to congenital abnormalities, 1960 and 1980. Public Health Report 102:171-81

[3] American College of Obstetrics and Gynaecologists (ACOG): Committee Opinion, 2017

Invitae Carrier Screening Options

Invitae offers three pre-set carrier screening panels:

	Pan-Ethnic	Broad Pan-Ethnic	Comprehensive
Number of genes	3	46	287
Number of X-linked disorders	1	5	21

These pre-set panels are customisable. The number of genes per panel are correct at the time of print, but may increase with time.

There is an option of including 13 additional add-on genes (to any panel) which include prevalent and highly variable disorders.

High detection rates = ~99% for most genes

1. Invitae Pan-Ethnic Carrier Screen

The Invitae Pan-Ethnic Carrier Screen includes **3 genes** associated with cystic fibrosis (CF), spinal muscular atrophy (SMA), and fragile X syndrome. These are common, severe disorders seen across all ethnicities.

Carrier rates (based on Invitae internal data n=140 000):

- 5.6% positive rate
- 1.4% at-risk couple rate

2. Invitae Broad Pan-Ethnic Carrier Screen

The Invitae Broad Pan-Ethnic Carrier Screen includes **46 genes** associated with disorders that may have a severe presentation and are prevalent across all ethnicities.

Appropriate for couples of all ethnicities who want to screen for common and severe disorders. The 8 autosomal recessive conditions the ACMG recommends screening for in Ashkenazi Jewish couples are included in this panel.

Carrier rates (based on Invitae internal data n=145 000):

- 30 - 50% positive rate
- 1.4 - 2% at-risk couple rate

3. Invitae Comprehensive Carrier Screen

The Comprehensive Carrier Screen panel includes **287 genes**. Appropriate for couples of all ethnicities who want an expanded assessment of their risk of having an affected child. The 8 autosomal recessive conditions the ACMG recommends screening for in Ashkenazi Jewish couples are included in this panel.

Carrier rates (based on Invitae internal data n=5000 and publications):

- 70% positive rate
- 2 – 2.5% at-risk couple rate

Please visit the Invitae website for more information about the genes and conditions included in the above carrier screening options:

https://www.invitae.com/en/physician/category/CAT000239/#category-content-CAT000241

Results

The Invitae report only includes **pathogenic and likely pathogenic variants** (variants of uncertain significance are not reported). The results are presented in a patient-facing report that is clear and easy to understand as well as providing interactive information on the Invitae web portal if the result is released to the patient by the referring clinician.

For positive results, there is a summary page for the disorder in question, which explains the clinical features and inheritance pattern.

For negative results, there is a residual risk table included – i.e. what are the chances that a patient could still be a carrier after testing negative. These risks are calculated using the carrier frequency of a condition and the detection rates. The residual risk is never zero, as there is always a small chance of being a carrier even after a negative result.

PathCare will log the sample on your behalf and Invitae will email a link to access the report to the email of the referring clinician.

In the event of identifying **both partners as carriers for the same gene/condition,** preimplantation genetic testing or prenatal testing should be discussed with the couple as well as other reproductive options. Genetic counselling is recommended. **Prenatal testing in our local context may take months to optimise and the availability for each condition included in this screen cannot be guaranteed.**

Cost

The cost of any Invitae carrier screen (regardless of the number of genes tested) is **250 US Dollars.** If both the patient and their partner undergo carrier screening the cost for the couple is **350 US Dollars** (discounted partner price of 100 US Dollars). As this is a patient-pay option, Invitae bills the patient directly for these tests.

PathCare charges an international courier fee (R811) and handling fee (R500) per couple which is paid upfront at the depot when providing the sample.

If your patient is found to be a carrier, testing of their partner is indicated to provide appropriate risks for their future or current pregnancy. Clinicians may choose to test both partners simultaneously (especially if there are timing concerns in the context of a pregnancy) or sequentially. The cost for the partner's test remains 100 US Dollars regardless of timing.

Sample

Saliva samples are sent to Invitae in **specialised Saliva Collection Kits**. These can be arranged for your patient and their partner at their closest PathCare depot. Please let our genetics team know if you are ordering this option for your patient and we will arrange sample collection.

Turnaround Time

The turnaround time for Invitae tests is **10-21 calendar days** (14 days on average) once the sample arrives at Invitae. The results will be emailed to the referring clinician directly. As this may be in the context of a pregnancy, please be advised that you may want to send both your patient and their partner's samples at the same time to avoid delays.

Please see the "Information for referring clinicians and genetic counsellors" document for more information on how to order.

Genetic Counselling

As suggested by international guidelines, pre- and post-test genetic counselling is strongly recommended for any genetic testing referrals. A genetic counsellor will be able to identify those at risk and facilitate further testing, particularly in the case of positive carrier screening results, where there may be implications for other family members.

Please contact our genetics team for the contact details of an HPCSA-registered genetic counsellor who can arrange to see your patient. We understand that there are limited genetic counselling services in South Africa, however, most genetic counsellors would be able to arrange telephonic/Skype consultations if necessary.

Please feel free to contact our genetics team if you have any questions on 021 596 3655 or geneticconsult@pathcare.org

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