Genetic screening prior to conception
To what extent?

Dr Saskia BULK
Dr Aimé LUMAKA

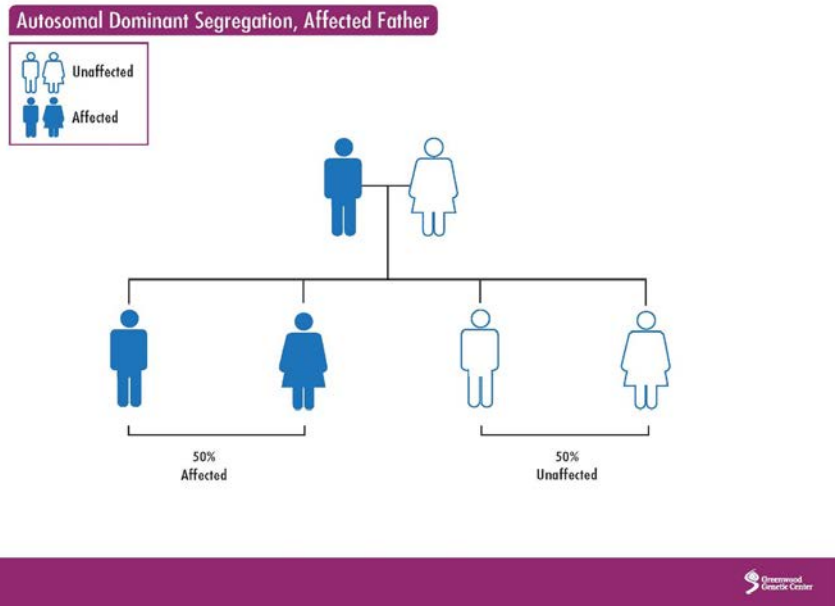
Extended Carrier Screening

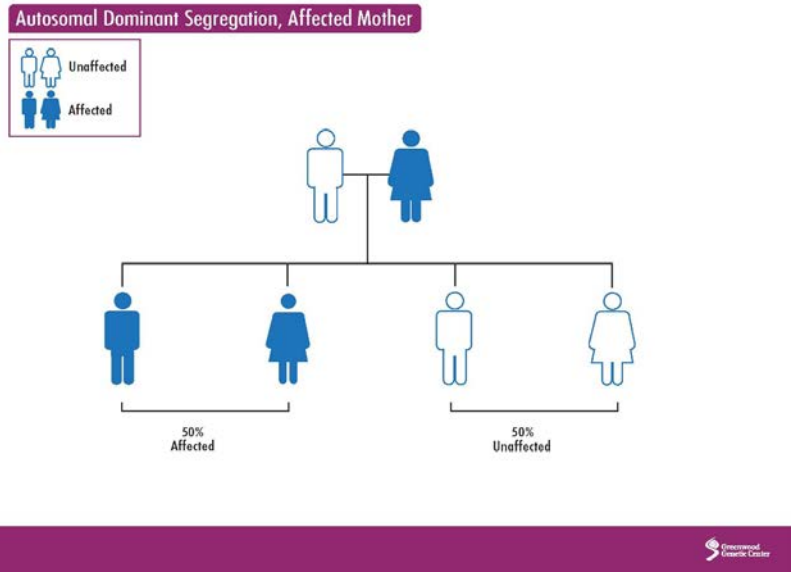
- Carrier screening for inherited conditions is an important component of preconception and prenatal care
- Purpose: to identify couples at risk for passing a genetic conditon to their offspring
- Goal: to reduce perinatal and infantile morbidity and mortality
- Facilitate early provision of therapeutic of profylactic measures (PND, PGD)

Extended Carrier Screening

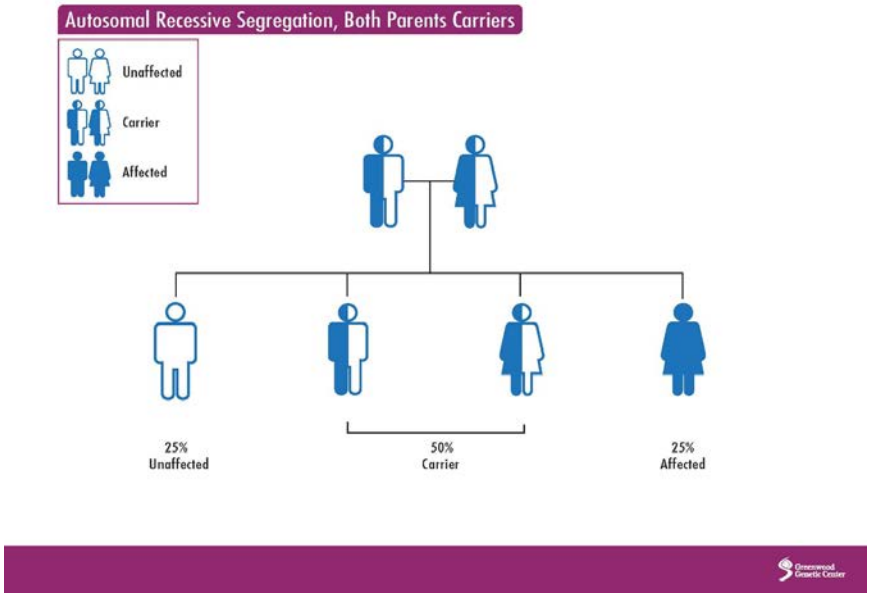
Genetic carrier testing is <u>not</u>

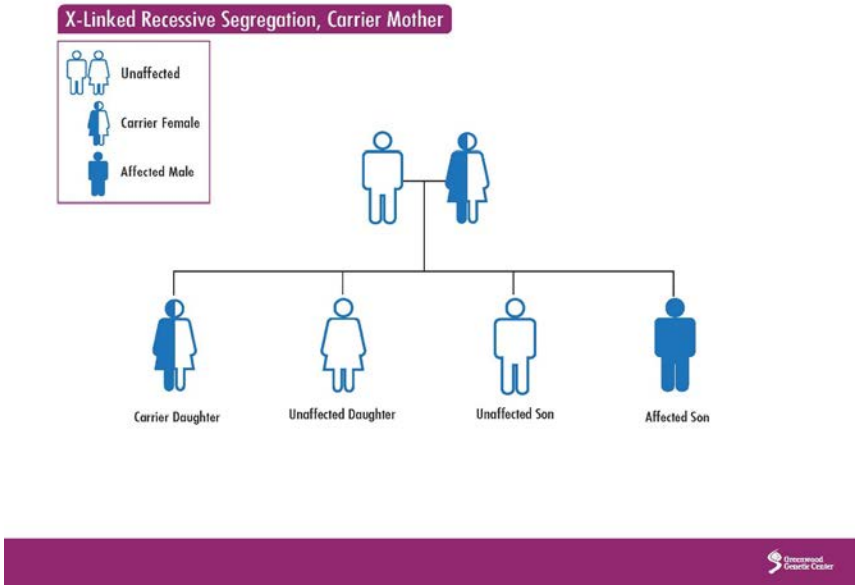
- Testing for autosomal dominant conditions
- Risk ½ (50%)
- Symptomatic or presymptomatic testing





Extended Carrier Screening





Autosomal recessive conditions
Risk ¼ (25%)

X-linked conditions
Risk ½ (50%) for boys

Extended Carrier Screening

- Worldwide, consanguinity for 10% of couples (consanguineous parents or themselves)
- In certain populations, 50 to 60% of couples are of consanguineous origin (*eg*., Pakistan)

- A first cousin liaison is associated with a 2,0 - 2,5% increase in risk

Extended Carrier Screening

- AR diseases cause serious morbidity and/or mortality in at least 25 out of 10.000 children
- Most persons found to be a carrier of an AR disease have a negative family history (given the low statistical likelihood of mating with another nonrelated carrier)
  - CFTR: 1/20*1/20*1/4 = 1/1600 ~ 0,06%
  - Cascade screening (testing relatives of identified carriers) does not diagnose carrier status in an estimated 97.5% (Krawczak et al)

Informed reproductive choices

- PGD (preimplantation genetic testing, « embryo selection »)
- PND (prenatal testing, and abortion if affected)

Accepting the risk

Refraining from having children

Adoption

Change of partner (*eg*., Dor Yeshorim programme)

Sperm/egg donation

Extended Carrier Screening

Dor Yeshorim

- Debilitating and recessive genetic diseases, based on severity of symptoms and frequency of disease
- Most commonly occurring in the Jewish population
- Aimed at ethnic groups (*eg*., Ashkenazim, Sephardim)
- Including CFTR and SMN1

Extended Carrier Screening

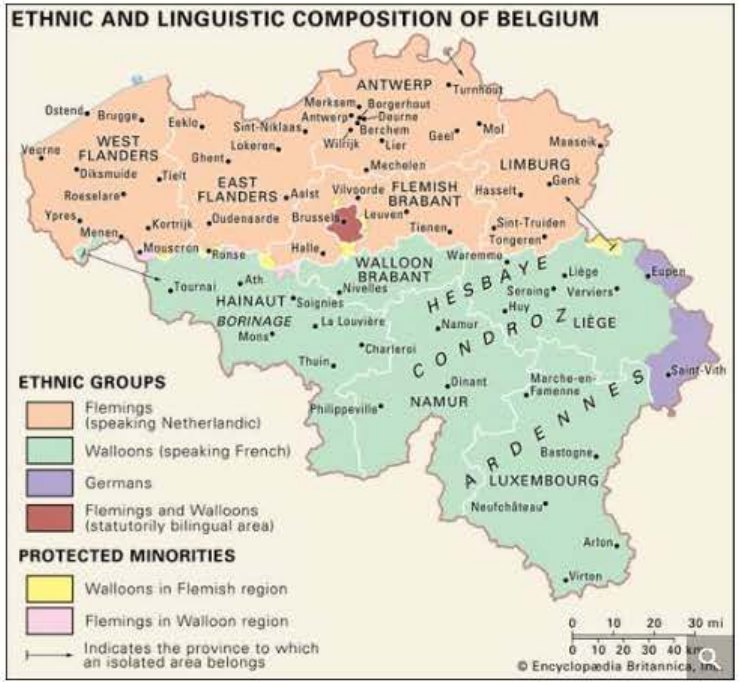
Population-at-risk testing

- Consanguineous relations
- Genetic isolates (*eg*., German-speaking community in Belgium)
- Parents with an affected child
- With or without known diagnosis

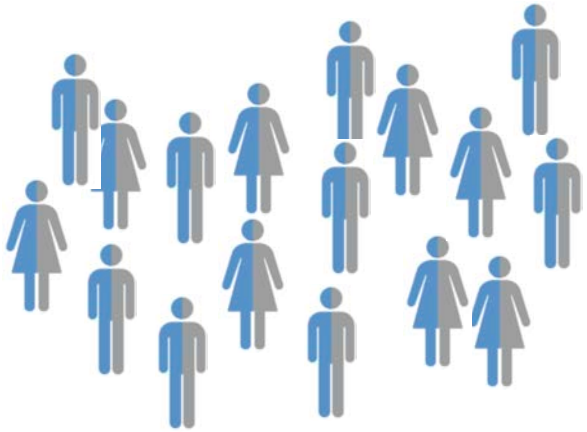
Ethnicity-based testing

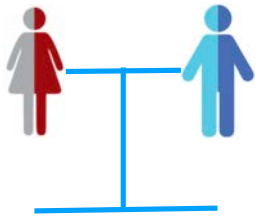
- Mediterranean origin
- Western-European origin

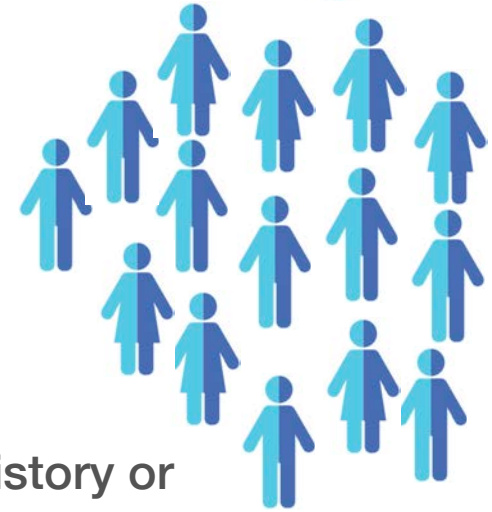
Population-based screening



Comprehensive screening versus targeted testing

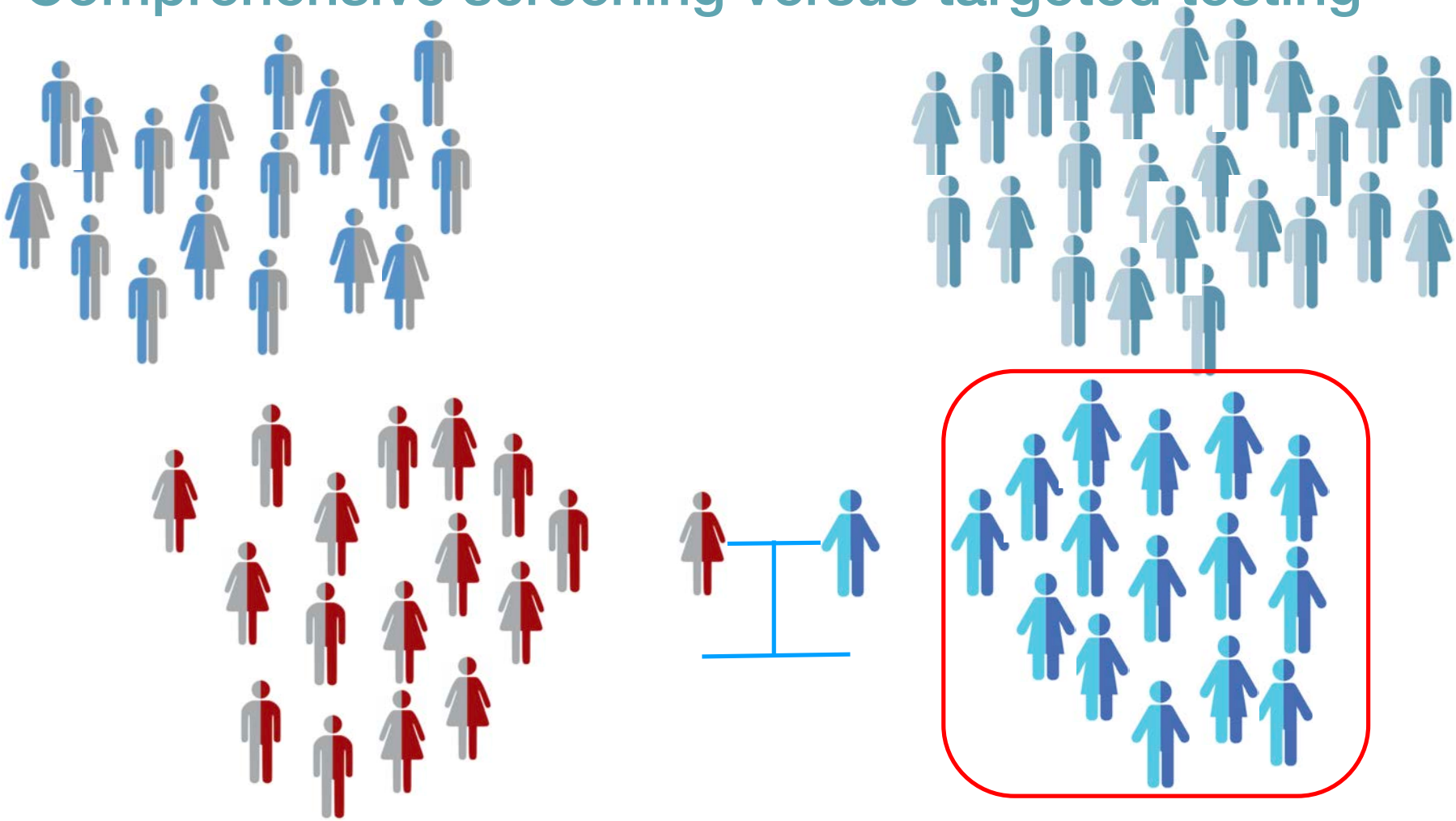






À la carte:
Selective, based on history or partner's result.
Expensive, discriminatory

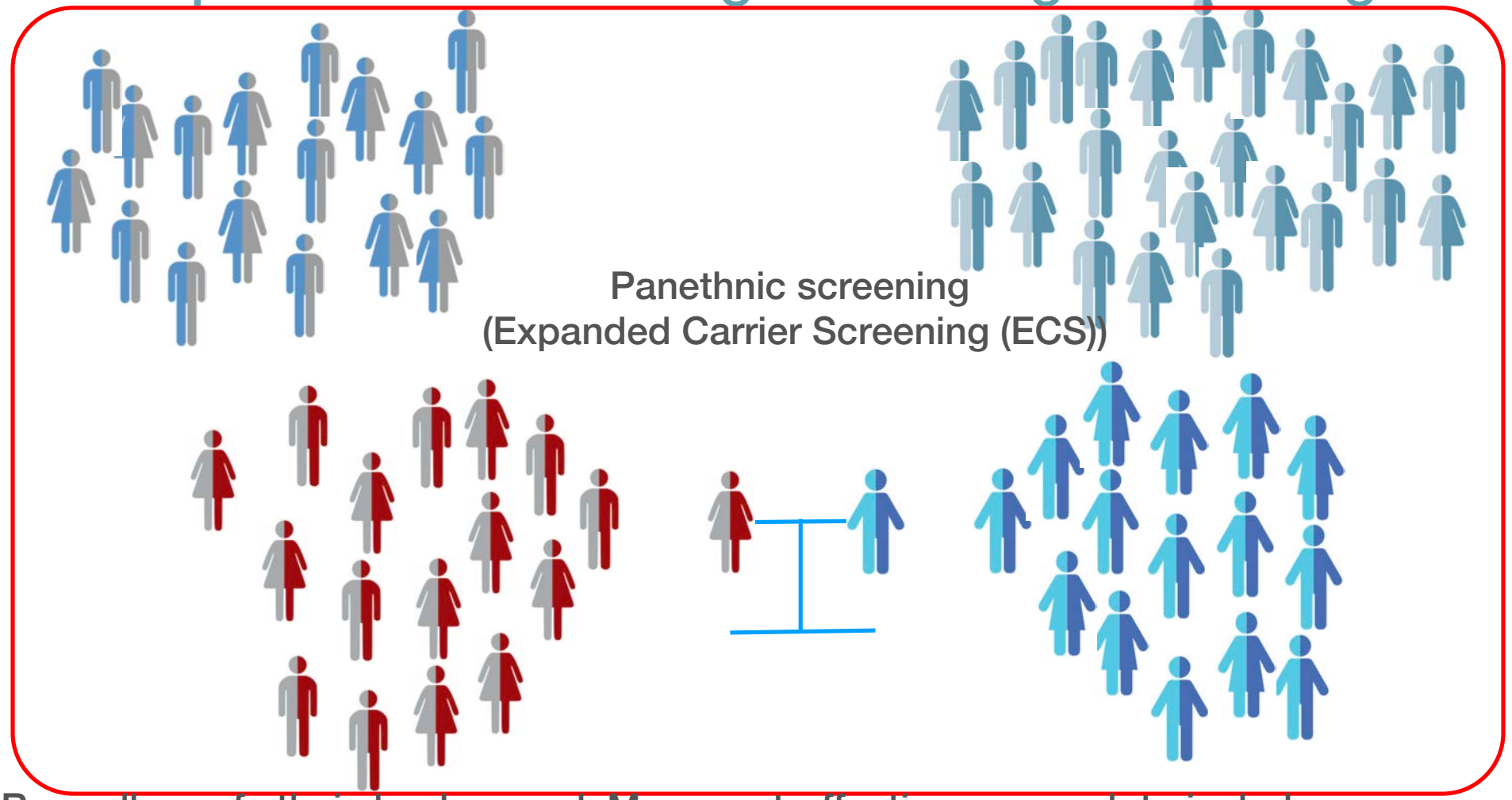
Comprehensive screening versus targeted testing



Ethnicity based:

Population-specific diseases. Known mutations (eg., Dor Yeshorim)
But ethnic background not always known.

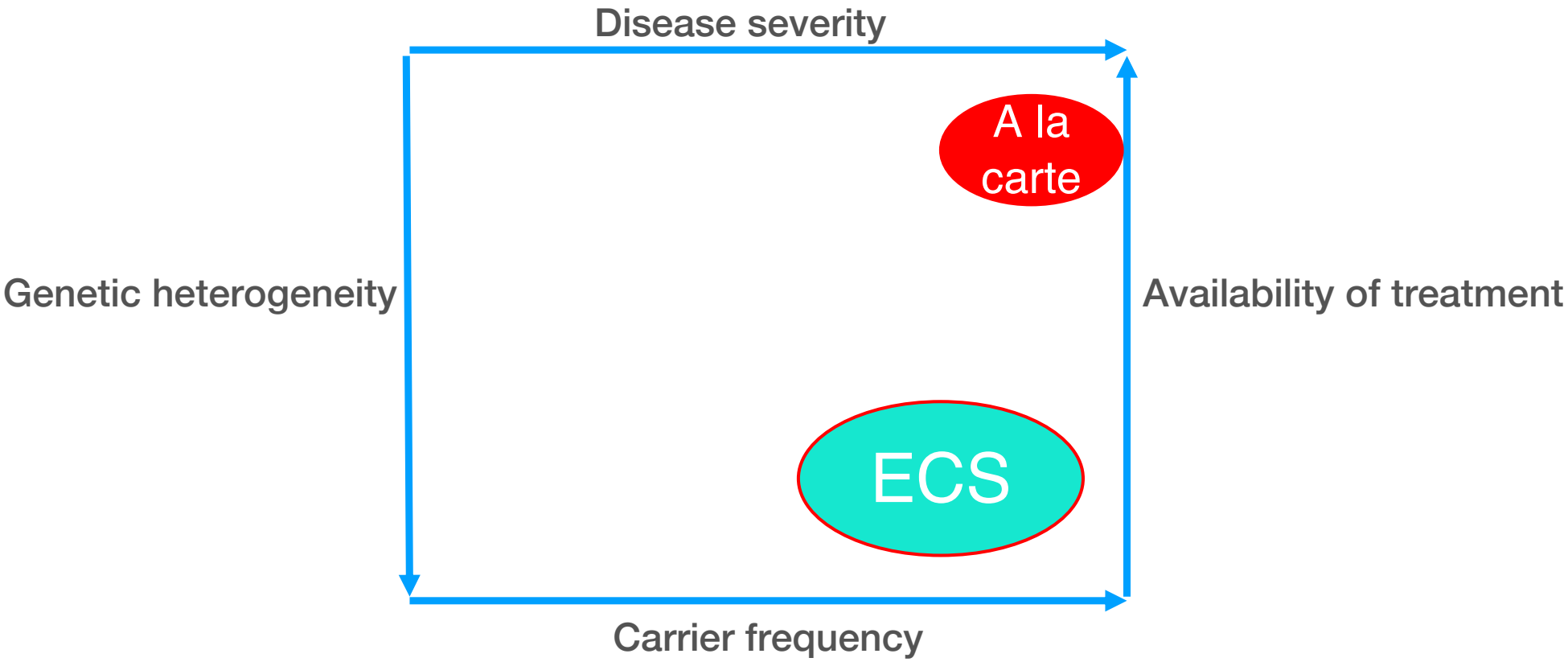
Comprehensive screening versus targeted testing



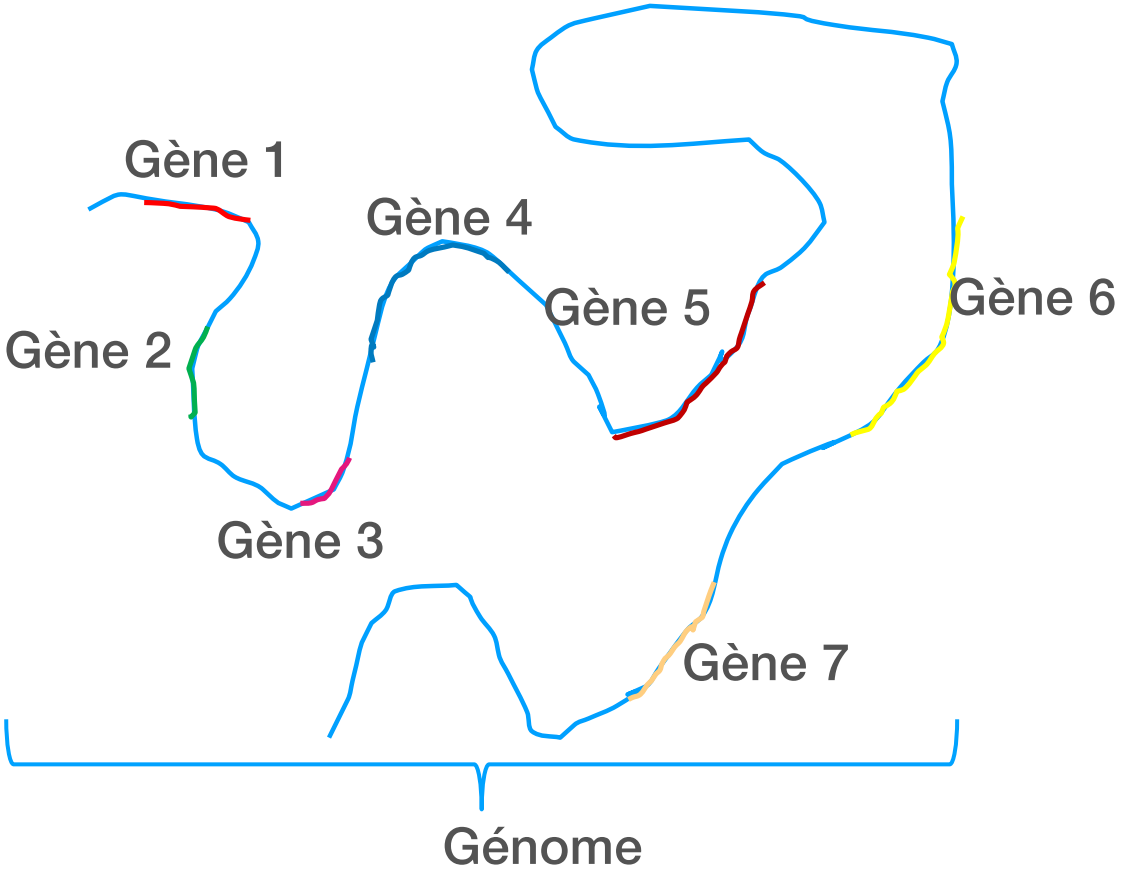
Regardless of ethnic background. More cost-effective approach to include more recessive disorders

BUT: complexity for interpretation and does not necessarily increase reproductive autonomy

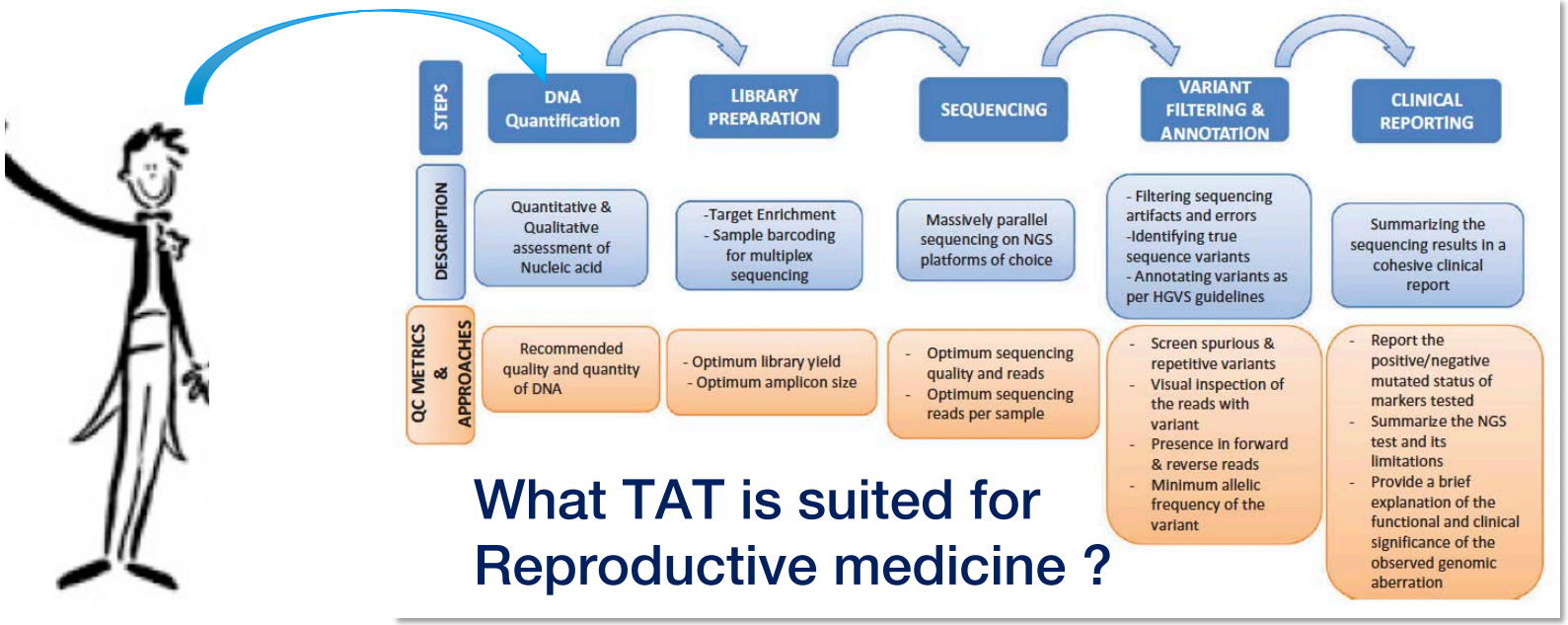
Disease selection



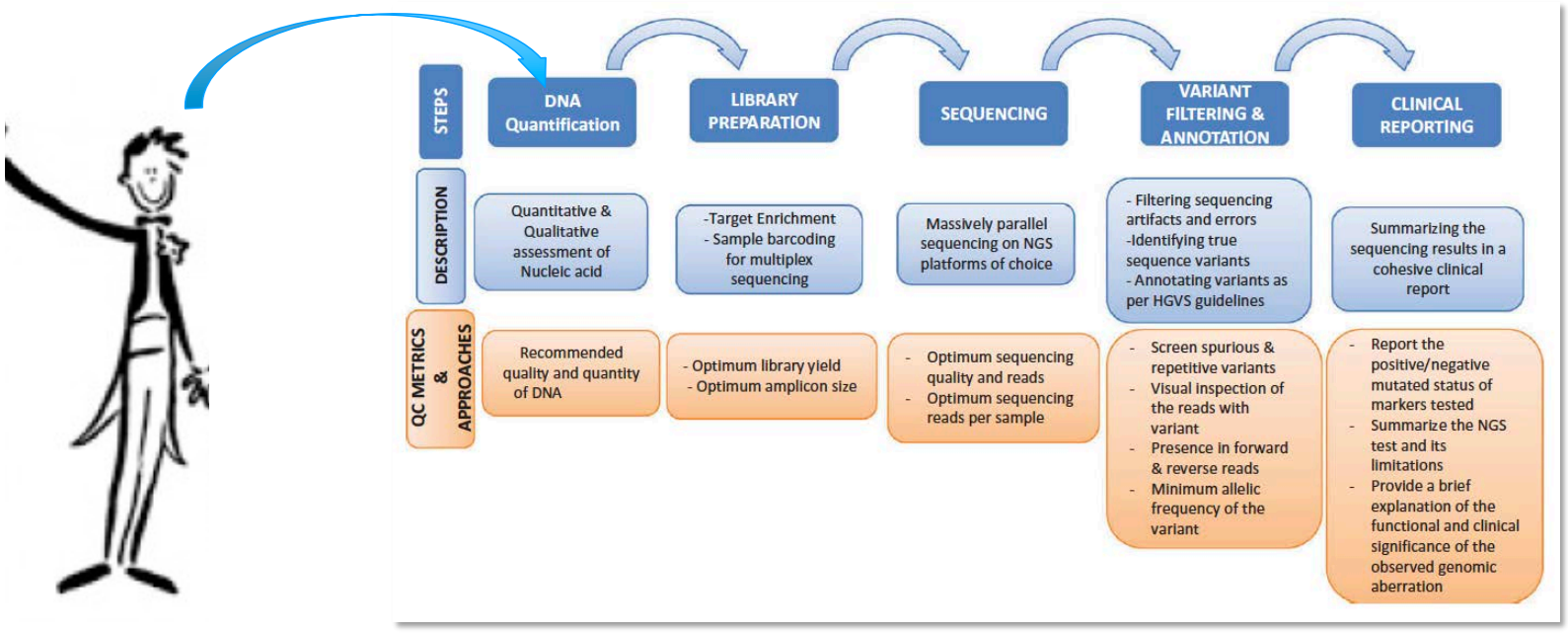
Next Generation Sequencing (NGS)



NGS analysis is a multistep process



NGS analysis is a multistep process



Exome testing in a diagnostic setting

- Phenotype
- Medical history of the patient
- Family history

Carrier screening: interpretation of variants

- No index case (no phenotype)
- No medical history (no phenotype)
- No family history

Genet Med. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.

	Benign		Pathogenic			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very Strong**
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Figure 1. Evidence Framework

Extended Carrier Screening

Problems of a negative test

- Repeat disorders (*eg*., FMR1)
- Deletions/duplications
- Intronic mutations
- Unknown genes
- Variations of unknown significance or Mosaicism

Problems of a positive test

- Diagnosis of unrecognized disease
- Unclear value for some disorders (*eg*., MTHFR testing)
- Certain genes have a phenotype in both heterozygous and bi-allelic state
  - ✓ BRCA2: Breast and ovarian cancer versus Fanconi anemia
  - ✓ ATM: Breast cancer versus ataxia teleangiectasia

Indication for pre- and posttest counseling

- Correct paternity (and maternity) is essential
- Negative testing reduces but does not eliminate risk to the offspring
- Carrier status rarely has medical consequence for the carrier
- A positive family history is an indication for referral
- A test could be diagnostic or presymptomatic

How to choose the right one?

Gamete donation

- Karyotyping
- CFTR
- Thallasemia and sickle cell anemia if indicated
- SMN1?
- FMR1?

Exclusion of healthy carriers

Extended Carrier Screening

- Gamete donation no longer possible if healthy carriers are excluded from donation

- Everybody is a healthy carrier of multiple autosomal recessive disorders

Extended Carrier Screening

- Donor-recipient matching
- 200 genes tested, 3% of couples non-matching

- Donor testing of a limited panel with exclusion of all healthy carriers
- But what genes will be included?

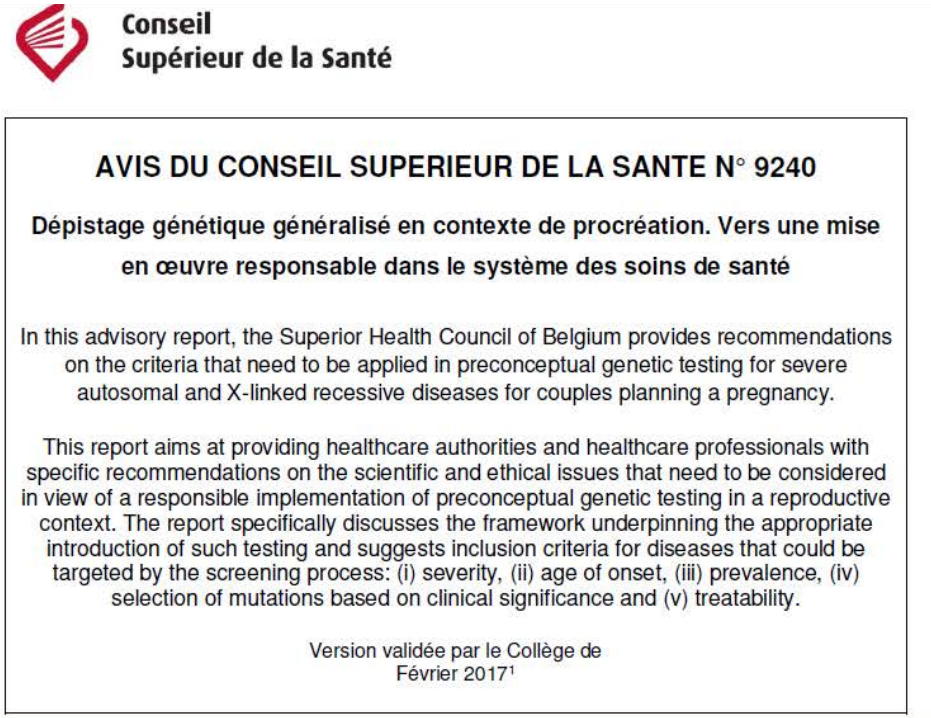
- Required testing of minimal panel with optional testing of extended panel

- Exclusion of dominant and X-linked disorders and matching of recessive disorders
- Eugenetics?

- Informed consent and counseling of donors necessary

Extended Carrier Screening

- Available in Belgium as of April, 2020 (estimation)
- Population-based, comprehensive testing (and therefore also including ‘mild’ conditions)
- Complementary to the screening for CFTR and SMN1 (and FMR1)
- 1400€ per couple



Conseil
Supérieur de la Santé

AVIS DU CONSEIL SUPERIEUR DE LA SANTE N° 9240

Dépistage génétique généralisé en contexte de procréation. Vers une mise en œuvre responsable dans le système des soins de santé

In this advisory report, the Superior Health Council of Belgium provides recommendations on the criteria that need to be applied in preconceptual genetic testing for severe autosomal and X-linked recessive diseases for couples planning a pregnancy.

This report aims at providing healthcare authorities and healthcare professionals with specific recommendations on the scientific and ethical issues that need to be considered in view of a responsible implementation of preconceptual genetic testing in a reproductive context. The report specifically discusses the framework underpinning the appropriate introduction of such testing and suggests inclusion criteria for diseases that could be targeted by the screening process: (i) severity, (ii) age of onset, (iii) prevalence, (iv) selection of mutations based on clinical significance and (v) treatability.

Version validée par le Collège de
Février 2017[1]

Extended Carrier Screening

In conclusion

- Extended carrier screening will be available in the foreseeable future
- Practical, ethical and societal considerations
- For reproductive medicine, decisions will have to be made if, how and/oir what to implement in daily practice

Genetic screening prior to conception
To what to extend?

saskia.bulk@chuliege.be
aime.lumaka@uliege.be