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Title:

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Date:

2020-02-01

Citation:

Delatycki, M. B., Alkuraya, F., Archibald, A., Castellani, C., Cornel, M., Grody, W. W., Henneman, L., Ioannides, A. S., Kirk, E., Laing, N., Lucassen, A., Massie, J., Schuurmans, J., Thong, M. K., van Langen, I. & Zlotogora, J. (2020). International perspectives on the implementation of reproductive carrier screening. *Prenatal Diagnosis*, 40 (3), pp.301-310. <https://doi.org/10.1002/pd.5611>.

Persistent Link:

<https://hdl.handle.net/11343/286676>

International perspectives on the implementation of reproductive carrier screening

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/pd.5611](https://doi.org/10.1002/pd.5611)

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Running head: Global reproductive carrier screening

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The authors have no conflicts of interest

What's already known about this topic?

- Reproductive carrier screening is available for an ever increasing number of autosomal recessive and X-linked recessive disorders.
- Reproductive carrier screening takes place in different ways in different jurisdictions with some Government funding and some user-pays.

What does this study add?

- This review identifies many different approaches to reproductive carrier screening in different countries.
- This largely relates to geographical variation in carrier frequencies of genetic conditions and local healthcare, financial, cultural and religious factors.

Word count- 4812

Tables- 1

Figures- 0

Abstract

Reproductive carrier screening started in some countries in the 1970s for hemoglobinopathies and Tay-Sachs disease. Cystic fibrosis carrier screening became possible in the late 1980s and with technical advances, screening of an ever increasing number of genes has become possible. The goal of carrier screening is to inform people about their risk of having children with autosomal recessive and X-linked recessive disorders, to allow for informed decision making about reproductive options. The consequence may be a decrease in the birth prevalence of these conditions, which has occurred in several countries for some conditions. Different programs target different groups (high school, premarital, couples before conception, couples attending fertility clinics, pregnant women) as does the governance structure (public health initiative, user pays). Ancestry based offers of screening are being replaced by expanded carrier screening panels with multiple genes that is independent of ancestry. This review describes screening in Australia, Cyprus, Israel, Italy, Malaysia, Netherlands, Saudi Arabia, United Kingdom and United States of America. It provides an insight into the enormous variability in how reproductive carrier screening is offered across the globe. This largely relates to geographical variation in carrier frequencies of genetic conditions and local healthcare, financial, cultural and religious factors.

Introduction

Reproductive carrier screening (RCS) is the process of testing individuals and couples for their risk of having children with autosomal recessive and X-linked recessive conditions.¹ Such screening can be done prior to pregnancy or in the early stages of pregnancy. It can be offered to individuals prior to forming a relationship such as through high school screening programs, to individuals prior to an arranged marriage such as through the Dor Yeshorim program and to couples prior to becoming pregnant or in early pregnancy.² When both members of a couple are carriers of an autosomal recessive condition or a woman is a carrier of an X-linked condition there is an increased chance (generally 1 in 4) of having an affected child. Couples with an increased risk have a number of reproductive options to avoid or prepare for having a child with that condition depending on their choices. These include testing a pregnancy with the option of terminating those that are affected by the genetic condition or testing embryos produced by IVF (preimplantation genetic testing for monogenic disorders, PGT-M). RCS provides people at increased risk of having a child with a genetic condition with reproductive autonomy in relation to whether or not to take steps to avoid having a child with that condition.

Reproductive carrier screening became possible in the 1970s. This preceded the ability to test directly for genetic mutations by more than a decade. Carriers of some conditions have differences in blood test parameters that allow them to be identified as heterozygotes.³ This includes hemoglobinopathies such as beta-thalassemia and sickle cell disease. Carriers of these disorders have reduced mean corpuscular volume (MCV) and changes in hemoglobin electrophoresis indices. It was also possible to screen for Tay-Sachs disease (TSD), a lethal neurodegenerative condition.⁴ TSD is caused by mutations in the gene that encodes the

hexosaminidase A enzyme (*HEXA*). Carriers of TSD almost always have lower levels of hexosaminidase A than non-carriers.

In the late 1980s it became possible to identify carriers by genetic testing. Cystic fibrosis (CF) screening was among the first conditions for which screening was offered by genetic testing⁵ following identification of mutations in *CFTR* as the cause. In addition, some TSD programs changed from enzymatic testing to molecular testing which has the advantage of being a less complex assay that does not require a blood sample.⁶ From there, screening for an increasing number of autosomal recessive and X-linked recessive conditions has become possible.

Initially, screening focused on ethnic groups at higher risk of specific genetic disorders. For example screening for hemoglobinopathies was commonly offered to those from Mediterranean regions, Africa and Asia. TSD screening programs were introduced in Ashkenazi Jewish communities and CF screening was increasingly offered to those of European descent.

With the advent of massively parallel sequencing (also called next-generation sequencing), carrier screening has become possible for hundreds of conditions relatively cheaply.⁷ This makes carrier screening more attractive than single gene mutation testing of the past. The new screening technology is referred to as expanded carrier screening (ECS). ECS removes the need for ethnic specific gene mutation panels which in the past raised concerns about discrimination.⁸ Such screening also required the individual and health professional to recognise the ethnicity of that person which is sometimes complex.⁹ One concern about ECS

that has been raised is in relation to the ability of people to provide informed consent for testing for multiple conditions.¹⁰

RCS has been adopted in various centres and/or countries, often in an ad hoc manner. In most jurisdictions it is available to those able to pay with relatively few national funded programs. In this review we provide information about the current screening programs in nine countries/regions. It is not possible to include all countries in such a review but we have attempted to draw together experiences from across the world highlighting considerations arising from differing healthcare systems, cultures and religions.¹¹ We have included countries from multiple regions and counties where carrier screening has been conducted in different ways to address local challenges such as those posed by funding constraints and religious requirements. A summary of RCS in these nine countries/regions and the availability of reproductive options is presented in Table 1.

As this is a review article, no approval from a Human Research Ethics Committee was required. Similarly there are no original data presented in this review so data sharing is not relevant to this article.

Australia

In Australia, reproductive carrier screening began in an ad hoc way in the 1970s with hemoglobinopathy screening.¹² Post World War 2 migration from Mediterranean countries meant the number of carriers of beta-thalassemia increased in the Australian population, which had hitherto been predominantly indigenous and Northern European. From the late 1970s migration from South East Asia increased the number of alpha-thalassemia carriers. Hemoglobinopathy screening was initially inconsistent, since it relied on red blood cell parameter testing. Nevertheless, the live birth prevalence of thalassemia dropped substantially after introduction of screening.¹³ Screening for hemoglobinopathy carrier status is Government funded.

Systematic TSD screening began in Jewish high schools (offered to those in the penultimate year of school), and communities more generally, in Sydney (1995)¹⁴ and Melbourne (1997).¹⁵ The high school program initially incurred a cost and testing was from a blood sample. From 1998 testing was free with collection by cheek swab, the combination increasing participation to 96%.⁶ In 2008, the program was increased to include seven conditions (TSD, CF, Canavan disease, Bloom syndrome, Nieman Pick disease type A, Fanconi anaemia and familial dysautonomia).¹⁶ The Melbourne program ceased in 2016 since it was considered that by the time most students will be planning a family, much broader screening will be available than the screening that was being offered.²

CF carrier screening in people with no family history of the disorder began in Victoria in 2006 with screening offered pre and in the early stages of pregnancy, largely by obstetricians and general practitioners (GPs).¹⁷ Up until that point, only prospective parents with a family

history of CF could access testing. The initial CF carrier screening program was developed on a fee-for-service basis using a cheek swab mailed to the testing laboratory and by 2010 there were approximately 3000 screening tests per year (birth rate in Victoria about 80,000/year).¹⁸ From 2012, the program was expanded to include spinal muscular atrophy (SMA) and fragile X syndrome (FXS) with around 1 in 20 women screened being a carrier of at least one of the conditions.¹⁹

From 2014 the opportunity for ECS became possible through private providers. In 2019 the Royal Australian and New Zealand College of Obstetricians and Gynaecologists published guidelines recommending that at a minimum, information on carrier screening for hemoglobinopathies, CF, SMA and FXS be offered to women preconception or in the first trimester with consideration given to offering ECS.²⁰ Between 2019-2021 there will be a Government funded trial of reproductive carrier screening for >1000 genes in 10,000 couples Australia-wide.² Genes were selected based on the severity of conditions. The aim of this research project is to test the feasibility of a National, Government-funded reproductive carrier screening program.

Genetic counseling, prenatal diagnosis and pregnancy termination is Government funded and is free of charge to couples found to have an increased risk of having a child with one of the conditions for which screening is done. Whilst there is some Government funding for IVF, PGT-M currently incurs considerable out of pocket expenses in Australia.

Cyprus

The carrier rate for beta-thalassemia mutations in Cyprus is about 1 in 8 and is one of the highest in the world.²¹ It is hypothesized that this reflects the survival advantage of thalassemia carriers for malaria, which was once endemic on the island. By the late 1960s, beta-thalassemia major was established as a major public health challenge in Cyprus. Affected individuals faced a debilitating disease associated with significant morbidity and mortality. On the other hand, the management of beta-thalassemia included regular blood transfusions and the use of iron chelation therapy, that resulted in increasing strain on national healthcare resources.

In the early 1970s, the Government commissioned a report on the projected impact of beta-thalassemia on healthcare delivery in Cyprus.²² Following that report, the first population screening program in Cyprus for beta-thalassemia carriers was launched in 1973 based on a combination of hemoglobin electrophoresis and the assessment of hematological indices. The campaign focused primarily on high school students and army conscripts, as well as relatives of affected individuals.²³ By 1977, prenatal diagnosis could be offered²⁴ and screening shifted to prospective parents before or during pregnancy. By the early 1980s, there was a drive towards a more effective screening method for individuals of reproductive age leading to the introduction of the premarital certificate. In essence, couples seeking to marry through the Greek Orthodox Church were asked by Church authorities to present evidence that they had been screened and received relevant counseling at the National Thalassaemia Centre. Although this screening approach was not mandatory, the uptake was very high and the choice of prenatal diagnosis and termination of affected pregnancies resulted in a dramatic reduction in the birth prevalence of beta-thalassemia.²⁵⁻²⁷

Over the years, state authorities have played a more prominent role in informing couples about screening, in view of an increasing number of civil marriages. Initial post-test counseling takes place at the specialist National Centre and this also covers alpha-thalassemia and sickle cell disease. Prospective parents may consider the options of PGT-M or prenatal diagnosis and genetic testing.

In addition to hemoglobinopathy screening, a national screening programme for the prevention of Friedreich ataxia has been running since 2011.²⁸ It is offered to individuals of child bearing age who originate from the Paphos district of Cyprus and is based on the high frequency of carriers in this section of the population which is estimated to be about 1 in 11.²⁹ Referrals are made by primary care doctors or obstetricians and testing is for the common GAA repeat expansion in intron 1 of the *FXN* gene.

Israel

A carrier-screening program among Ashkenazi Jews to detect couples at risk for having children with TSD was organized and funded by the Israeli Ministry of Health in 1980.³⁰ Later, a beta-thalassemia carrier screening program was implemented among Arabs, Druze and Jewish communities. Since then, the carrier-screening program has been under the aegis of the Ministry of Health and has gradually expanded.³¹ In 2002, the first expansion was to include severe diseases with a frequency of 1 in 1000 or higher, targeted to local Arab and Druze communities (villages/tribes). In 2008 the national program was further expanded to include familial dysautonomia for Ashkenazi Jews and CF for the whole population. Since January 2013, the program includes carrier screening for all common severe diseases as recommended by the Association of Israeli Medical Geneticists (carrier frequency >1 in 60 and/or disease frequency >1 in 15:000 live births) and is updated yearly. The carrier-screening program includes CF, SMA and FXS for the whole population and additional diseases according to the ethnicity of the couple. These additional carrier-screening tests are performed among Jews according to the community of origin and among Arabs and Druze according to the religion and the locality of origin or tribe among the Bedouins of the Negev. In 2013, where 171,444 babies were born in Israel, there were approximately 62,000 individuals screened in the national program.³¹

The recommended tests are free of charge for all the Israeli citizens and are performed either in genetic units, in the community or through the Dor Yeshorim program.³² The Dor Yeshorim program is designed specifically for ultra-orthodox Jews, where a couple have screening prior to an arranged marriage which goes ahead if both members of the couple are not carriers of the same recessive condition. In the general population, the recommendations and explanations before the tests are given by genetic counselors or medical personnel under the supervision of a

medical geneticist. The information includes the option to perform additional patient funded tests for less frequent or less severe diseases. Most often, the woman is tested first and if found to be a carrier her partner is tested. At-risk couples receive genetic counseling and may access prenatal diagnosis or PGT-M free of charge.

Italy

In Italy the history of carrier screening has mainly concerned thalassemia and CF. Neither has been implemented at the national level and both originated from regional health strategies. A structured policy for carrier detection was developed in areas where thalassemia is highly prevalent, like Sardinia, Sicily and the Po river delta.³³ CF is homogeneously distributed throughout Italy, but carrier screening has been more extensively offered and used in north-eastern Italy, following work by the University of Padua.³⁴ It is supported by the regional health system.

The first experiences in thalassemia carrier screening date back to the 1970s, when non-genetic tests were offered in high schools and, later, to young couples. These campaigns were well received by the local populations, who were generally aware of the prevalence and severity of the condition. Identification of carrier couples led to a dramatic reduction in the birth of affected children.³³ Today the test is mainly offered by obstetricians and GPs and the live-birth prevalence remains low, with a stable number of carrier couples accepting the risk of having affected children, possibly because of the better treatments available compared to the past such as oral iron chelation therapy.³³

Since 1993 CF carrier screening has been widely practiced in part of north-eastern Italy, although not in a formal setting. The test is usually offered by obstetricians and primary care physicians and performed in public or private laboratories. In 25 years more than 200,000 tests have been performed and more than 7,000 heterozygotes have been identified.

In the initial twenty years of CF carrier screening the live-birth prevalence decreased dramatically.^{35,36} However, since 2011 the number of carrier screening tests for CF has substantially decreased, likely a reflection of changes to local regulations for the test offer and reimbursement. There has been a concomitant increase in CF incidence,³⁷ confirming the inverse correlation between RCS and number of children born with CF.

The attitudes of the general population and health professionals towards CF carrier screening were investigated by two studies supported by the Italian Cystic Fibrosis Research Foundation. Three citizen juries, a method of deliberative democracy to engage citizens in health decision making, were in favour of screening. In addition, an online public consultation found that the general public (86%) and health workers (63%) believe that the National Health Service should provide CF RCS.^{38,39}

Malaysia (and other South East Asian countries)

The most common genetic diseases in Malaysia are alpha and beta thalassemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency where 1 in 15 and 1 in 29 of the population are carriers of each of these conditions respectively.^{40,41} There is newborn screening for G6PD and it has a good outcome if it is treated early. The molecular epidemiology of thalassemia is well characterized in the major urban areas although there are certain indigenous populations who have not been well studied.⁴² In addition, thanks to expanded newborn screening using tandem mass spectrometry, the epidemiology of inborn errors of metabolism (IEM) showed that while phenylketonuria, medium chain acyl CoA dehydrogenase (MCAD) deficiency and galactosaemia occur in Malaysia, they are relatively less common than other IEMs such as citrin deficiency and organic acidemias.⁴³

Prenatal diagnosis is available and termination of pregnancy is legal in Malaysia when the mother's health is at risk, but it may not be available due to the high cost as well as cultural, religious and other factors.⁴⁴ Instead of screening in early pregnancy, alternative population screening strategies are offered. For example, thalassemia screening is offered to high school students aged 15-16 years of age.⁴¹ In Malaysia, Singapore, Thailand and other countries, hematological indices are used to screen for thalassemia in cascade and premarital screening programs.⁴⁵ Experience from population carrier screening for a single disease such as thalassemia in Guangxi, China resulted in the reduction of birth of children with severe thalassemia from 2.5% (2009) to 0.6% (2017).⁴⁶ Expanding carrier screening from a single disorder to 11 monogenic diseases using next generation sequencing in 10,476 couples in China, showed that 27.5% of individuals without self-reported family history of disorders, were found to be carriers of at least one of the 11 conditions.⁴⁷ Shen and colleagues cautioned

that 94% of hypothetical East Asian fetuses affected by a genetic condition would be missed if screening only occurs for conditions in recommended guidelines.⁴⁶ It was instructive to note that a carrier prevalence study of 104 genes for 80 treatable inherited disorders in Singapore showed 6% of a cohort of 831 were carriers of 1 of 13 treatable inherited disorders with citrin deficiency and Wilson disease having the highest carrier frequencies.⁴⁸ This suggests that population-specific genomics data are needed before targeted RCS can be implemented in Asia.

Finally, genetic counseling is essential in supporting RCS. In Malaysia and many parts of South East Asia, genetics services are not widely available and there is lack of healthcare resources and allocation for RCS. Hence it is expected that RCS will be largely undertaken on a user-pays basis. In view of the above challenges, RCS will require further support and information before it can be implemented in Malaysia and many other parts of South East Asia.

Netherlands

In the Netherlands hemoglobinopathy screening first appeared in the 1970's.⁴⁹ At that time, in collaboration with the Dutch Caribbean island of Curacao, a pediatrics professor started scientific research on hemoglobinopathies in the northern city of Groningen. Meanwhile in Amsterdam, where more migrants lived, screening was offered to individuals at high risk attending the tropical medicine clinic. Ethnicity surfaced as the impeding factor. In the 1990's hemoglobinopathy screening was found to be "not opportune" due to low prevalence, lack of knowledge and fear of stigmatization.⁴⁹ Some primary care midwives offer hemoglobinopathy screening on an ad hoc basis.⁵⁰

The first pilot study on preconception CF carrier couple screening started in 1997 in the mid-western region of the Netherlands, where individuals aged 20-35 years were invited to participate.⁵¹ Invitation letters were sent by a Municipal Health Service or GP. Couples could visit an educational group session or go to their GP. The highest response rate was found for GP consultation (25%). The main reason for non-response was "lack of time to attend". In 2005 a combined offer of hemoglobinopathy and CF carrier screening based on ethnicity was sent to 9,453 individuals (20-35 years), including 50-60% non-Western immigrants, in eight districts of Amsterdam, out of whom 72 couples participated.⁵² In 2010 CF carrier screening was offered direct-to-consumer via a hospital website. The offer ended after six years because of the low uptake and the fact that it was not primarily used by people without a family history of CF.⁵³

In a genetically isolated population (village) in the northwest of the Netherlands, preconception carrier screening for five conditions more common in that community has been

offered since 2012.⁵⁴ Due to religious and social factors, most children are born to couples where both members are from the village. Prospective parents are at relatively high risk of having a child with one of five severe childhood disorders compared to the general population. The screening tests are offered through an outpatient clinic in collaboration with the local midwifery practice.

In the Netherlands, there are no private providers offering carrier testing. ECS has been made available to interested couples by Amsterdam University Medical Centers since 2016 and this covers 50 diseases. Interested couples register on the website for face-to-face genetic counseling. For some couples with higher *a priori* risk (e.g. Ashkenazi Jewish origin, consanguineous couples) genetic counseling and testing are partly reimbursed by health-insurance.

ECS was offered in an implementation pilot study in the Northern Netherlands in 2016.⁵⁵ Because research showed that health professionals and the public prefer testing by GPs,⁵⁶ this was the way the pre-test counseling and test were offered. Trained GPs from nine practices invited 4,295 female patients aged 18-40 to take part in free couple-based ECS. The pilot demonstrated that 14% of eligible couples accepted ECS offered by their GP and that this screening is feasible and does not lead to unacceptable anxiety. Currently those GPs are still offering this test to their patients on a fee-for service basis. .

Saudi Arabia

Saudi Arabia is the largest Middle Eastern country, with a population of nearly 30 million, almost two thirds of whom are Saudi citizens. Consanguinity among Saudi parents exceeds 50%. This, combined with nearly half a million births per year, translates into a vast number of infants affected by autosomal recessive conditions.⁵⁷ Saudi Arabia has the highest documented number of autosomal recessive disorders per capita, in the world.⁵⁷

The power of consanguinity loops to render both ancient (founder) and young deleterious recessive alleles homozygous cannot be overemphasized. Until recently, public health preventative strategies have focused solely on the perceived predominance of hemoglobinopathies (sickle cell disease and thalassemia). There has been a premarital screening program that has been in effect since 2004 but is limited to sickle cell disease and thalassemia.

Recent advances made possible by NGS has brought many other disorders to the spotlight. In Saudi Arabia, autosomal recessive causes of intellectual disability have been shown to be the single most common class of recessive diseases and these can be caused by both private and founder mutations.⁵⁸ Previous work, including a large study involving >2,200 families with phenotypes that represent the entire Mendelian landscape, has shown that founder mutations account for at least 40% of the mutation pool.⁵⁹

With thousands of such founder variants identified to date, and with the capacity to screen for them in a single genotyping assay relatively inexpensively, the time is now ripe for implementing a population-wide premarital screening program. Although this approach has

the drawback of missing private mutations that have not yet made it to the central Saudi mutation database, the ease of interpreting the results and the avoidance of variants of uncertain significance that are inevitable in a sequencing-based assay are clear advantages. This expanded premarital screening program will build on the existing national premarital screening program for sickle cell disease and thalassemia that has been in effect since 2004. Currently, an expanded premarital screening program is being piloted on a small number of prospective couples, to collect sufficient data before the official launch of the program in the near future.

United Kingdom

The UK comprises four (slightly different) National Health Services (NHS) for England, Scotland, Wales and Northern Ireland. Each of these services is free at the point of delivery and universally accessible to those ‘ordinarily’ resident in the UK. The National Screening Committee (UK NSC) advises the NHS in the four UK countries about all aspects of population screening and supports implementation of screening programs in general; its database of recommendations sets out over 100 conditions, including recommendations to screen for 30 conditions. Recommendations on whether to screen for a condition are based on internationally recognised criteria and a rigorous evidence review process.

Preconception or prenatal carrier testing for conditions which have a high prevalence in specific (ethnic) populations is available through a variety of clinical services (e.g. hematology, clinical genetics, general practice). Cascade screening in families where a diagnosis has already been made is also available.

Immigration from Commonwealth countries since the middle of the 20th century introduced increased prevalence of hemoglobinopathies: sickle cell disease from West-African countries and the Caribbean, and thalassaemia primarily from the Indian subcontinent. After ad hoc and inconsistent availability of hemoglobinopathy testing since the 1970s,⁶⁰ a national antenatal screening program for hemoglobinopathies to all pregnant women was recommended by the UK NSC and introduced in the early 2000s through Public Health England. NHS-funded TSD disease carrier screening has been available for people from Jewish ancestry since 1999.⁶¹

Several pilot studies for antenatal CF carrier screening were conducted in primary care or maternity hospitals in the 1990s,^{62,63} but this has not led to a national screening program for the general population. The UK NSC advised against population screening for CF in 2006 since, according to them, it did not meet Wilson and Jungner criteria.⁶⁴ Currently, the NSC is reviewing their recommendation regarding antenatal CF screening. Sickle-cell disease and CF are both part of the newborn screening program.⁶⁵

The 100,000 Genomes Project (100kGP) recruited NHS patients between 2014 and 2018 and offered a range of different carrier testing as an ‘additional finding’. Both parents of children recruited with a rare disease were offered such testing, with the aim of disclosing this as a couple result for autosomal recessive conditions⁶⁶ meaning that individual carrier states would not be disclosed but that the result would only be deemed ‘positive’ if both parents were found to be a carrier of the same condition. Despite gaining consent for such testing, the pipeline for carrier testing is not yet ready and no results have been disclosed at the time of writing. Although the NHS genomic medicine service has now replaced the 100kGP, it is not entirely clear what carrier testing will be offered when the service goes live later this year.

In an infertility setting, carrier screening for CF is part of the mandatory screening of potential gamete donors.⁶⁷ Carrier screening for other conditions is offered based on the donor’s ethnic background and family history of genetic conditions. A large section of fertility services fall outside the NHS and patients may be offered ECS, but there are no public data on numbers of people offered screening nor for uptake.

United States of America

Carrier screening in the USA began in the 1970s, with red cell parameter testing for hemoglobinopathies in African-Americans and enzymatic testing for TSD in Ashkenazi-Jews. While the latter has virtually eliminated TSD in Ashkenazi-Jews, the former was fraught with misconceptions, resentment and low uptake owing to flaws in roll-out and long-simmering cultural mistrust in the community.

Carrier screening at the DNA level first appeared in the USA in the form of targeted allele-specific detection of founder mutations in the Ashkenazi-Jewish population for disorders prevalent in that ethnic group (TSD and others).⁶⁸ The first pan-ethnic carrier screen at the DNA level was for CF, and the USA was the first country to implement nationwide population carrier screening for this disorder, in late 2001, based on recommendations developed by the American College of Medical Genetics (ACMG) and the American College of Obstetricians and Gynecologists (ACOG). The result was a policy to offer CF carrier screening to all couples of reproductive age, using a core mutation panel of 25 (later reduced to 23) *CFTR* variants.^{69,70} Almost immediately, however, commercial laboratories took it upon themselves to develop and market screening panels with larger numbers of *CFTR* mutations, even though this practice had been discouraged in the original recommendations.

Yet this was just a foretaste of what would come when NGS technologies enabled vastly expanded mutation screening, not just for CF but for hundreds of other recessive disorders as well. Indeed, the same objections could be raised about the inclusion of so many rare and poorly characterized disease genes as had been posited about inclusion of rare and poorly characterized *CFTR* variants. But the power of NGS was impossible to restrain, especially

when driven by commercial entities using ever larger disease panels as marketing tools. Ultimately, both ACMG and ACOG felt compelled to revisit their opinions on this matter, and recently both have relaxed their previous objections to such expansion, though couching their positions with such phrases as “may be offered” and “informed decision-making” and minimal carrier frequency requirements for disease inclusion.^{7,71-73} Unfortunately, some of the larger panels include disorders of adult onset, variable severity, low penetrance, or even no symptoms at all.⁷⁴ While there is no question that pan-ethnic ECS identifies more at-risk couples than ethnicity-specific targeted screening and has led to proposals to abandon strict carrier frequency thresholds for inclusion,^{75,76} it comes at a cost of added downstream testing and genetic counseling burden. And to make matters more complicated, the phenomenal popularity of direct-to-consumer genetic testing in the USA means that many patients come to the clinic with dubious carrier results in hand.

Lastly, one cannot ignore “the elephant in the room” surrounding prenatal services in the USA, with many states and the current federal administration constantly attempting to limit or eliminate access to pregnancy termination for any reason. Needless to say, if the option to terminate an affected pregnancy became illegal nationwide, the impetus and market for carrier screening – both standard and expanded – would be dramatically reduced, and the number of babies born with recessive genetic disorders would greatly increase.

What are the lessons learned from the international experience of RCS?

This review has shown the enormous variability in how RCS is offered across the globe. This largely relates to geographical variation in carrier frequencies of genetic conditions and local healthcare, financial, cultural and religious factors. Funding of RCS is variable but in many countries funded testing is minimal or only available to those with a high *a priori* risk. Additionally, access to genetic counseling and the offer of reproductive options also varies significantly. Collectively, this highlights inequity in access to RCS services. The ability to screen for ever increasing numbers of disorders by massively parallel sequencing will identify more at-risk couples but also raises considerable ethical issues about what conditions should be included in such screening and what should be done when variants of uncertain significance are identified. Society and Governments will need to continue to tackle the challenges that such technology raises in making decisions about what, if any, RCS is publicly funded. The “arms race” to offer the biggest panel of genes tested by companies that offer RCS will no doubt continue and will mean that individuals, couples, clinicians and healthcare systems will need to deal with the outcomes of this testing with ever increasing frequency.

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Table 1- Reproductive carrier screening and reproductive options in the nine different countries/regions

	Screening available	Termination of pregnancy for genetic disorders	Preimplantation genetic testing-monogenic disorders
Australia	Hemoglobinopathy screening Government funded. Other RCS in the absence of family history is user pays.	Legal and Government funded	Available, partially Government funded, partially user pays
Cyprus	Hemoglobinopathy and Friedreich ataxia screening are Government funded.	Legal and Government funded	Available, partially Government funded, partially user pays
Israel	Screening available for all severe diseases with an incidence higher than 1 in 15,000 and is Government funded	Legal and funded by National Health insurance	Available and funded by National Health insurance for a maximum of two children
Italy	Hemoglobinopathy screening Government funded. CF	Legal and Government	Available. Government

	screening in the absence of family history on a regional basis: in some areas regional Government funded with a nominal fee, in other areas user pays.	funded	funded in one Institution, user pays in several others.
Malaysia	Hemoglobinopathy screening Government funded. Other RCS is user pays.	Legal and Government funded at public hospitals if maternal health is at risk.	Available in selected private healthcare facilities and is user pays.
Netherlands	Hemoglobinopathy screening by HPLC/electrophoresis is reimbursed. Two hospitals offer expanded RCS (50-70 disorders) that is reimbursed in high-risk couples [†] but is user pays in the absence of family history or other high-risk indication. One hospital offers RCS (>1900 genes) for consanguineous couples that is reimbursed [†] . Screening in one specific Dutch founder	Legal up to 24 weeks pregnancy and Government funded.	Available, three cycles Government funded [†] .

	population is reimbursed [†] .		
Saudi Arabia	Hemoglobinopathy screening Government-mandated and funded. Targeted screening for familial mutations optional and Government-funded. Optional expanded carrier screening soon to be launched and Government-funded.	Legal and Government funded for strict indications and with a strict upper gestation limit.	Available and Government funded.
UK	Hemoglobinopathy and Tay-Sachs disease screening state-funded (and offered as population screen depending on ancestry). Other screening is state funded if family history of a condition. User pays for testing outside of National Health Service (NHS) eg fertility clinic	State-funded and legal but very restricted in Northern Ireland	Available for conditions licenced by Human Fertilisation and Embryology Authority, partially Government funded, partially user pays
USA	Mix of government, private insurance, and self-pay	Varies widely by state; where legal and available, government or insurance funded	Varies by state; some pay (in part) for PGT-M but not IVF; many procedures

		with prior authorization; other states have severe legal restrictions and no financial coverage; no federal Government funding under the Hyde Amendment	are self-pay
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*Reimbursement by health insurance. The mandatory insurance deductible in 2019 is € 385 per calendar year.