Review

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Carrier screening programs for rare diseases in developed countries and the case of Turkey: A systematic review

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SUMMARY Effective control of rare diseases requires health programs based on principles of protection and prevention. Carrier screening programs serve as preventive measures by identifying at-risk groups. This review examines the impact, implementation, advantages, and disadvantages of carrier screening, incorporating examples from ten countries: the United States, Canada, the United Kingdom, Israel, China, Australia, Italy, Germany, the Netherlands, and Turkey. Data on carrier screening and related policies were collected from July to November 2022 and presented in a tabular format using a coding system devised by the authors. Variability was observed in the diseases/disorders and populations screened, screening expenses, and government provision across the countries. The number of diseases/disorders examined, ranging from 3 to 47, was determined by committee guidelines, government resources, pilot studies, and national institute resources. Notably, carrier screening programs exhibited greater worldwide inconsistency compared to newborn screening programs. The comparative analysis of developed countries serves to guide emerging nations. To address inequalities at both local and global levels, there is a need to enhance the establishment, development, and implementation of carrier screening programs. Furthermore, cost analyses of screening should be conducted, and adequate funding should be allocated to countries. In conclusion, this review highlights the preventive potential of carrier screening for rare diseases and emphasizes the importance of improving carrier screening programs globally to achieve equitable healthcare outcomes.

Keywords rare disease prevention, carrier screening, preconception carrier screening, premarital screening, early diagnosis screening

1. Introduction

A rare disease is defined by the fact that it affects a small percentage of the population. However, there is no internationally recognized definition of rare diseases (*1,2*). In the European Union, rare diseases are classified as life-threatening or chronically debilitating diseases that affect fewer than 5 in 10,000 people. In the United States, rare diseases are recognized as diseases that affect fewer than 200,000 people, or 1 in 1500, and in Japan, fewer than 50,000 people, or 1 in 2,500 (*1-3*). The diagnosis and treatment of rare diseases, which are regarded as significant global health issues, are challenging and expensive (*2,4,5*).

2. The significance of health screenings in rare diseases

As with all diseases, in order to be successful in controlling rare diseases, the health program to be implemented must be based on the public health principles of protection and prevention. Preventive health services are classified into five groups/classes. These groups are named primordial, primary, secondary, tertiary, and quaternary prevention. In this context, the use of screening tests in a comprehensive rare disease control program is the most important tool or intervention. The primary goals of screening programs are as follows: *i*) Identifying at-risk individuals or carriers for screening, protecting them from the risk, and preventing disease onset (primary prevention); *ii*) Detecting and efficiently treating affected individuals at an early stage (at the asymptomatic/preclinical stage) (secondary prevention) (*2*).

The application of screenings in rare disease control

programs at this point has two purposes: *i*) identification of individuals who are carriers (autosomal recessive (AR) or heterozygous for a pathogenic or possible pathogenic variant in an X-linked disease; in other words, those who are at risk of having an affected offspring (primary prevention); and *ii*) ensuring that affected individuals are diagnosed at an early stage and receive the most appropriate and effective treatment (secondary prevention) (*2,6*) (Figure 1).

3. Who should be screened?

Over 40 years ago, Wilson and Jungner, on behalf of the World Health Organization (WHO), developed a gold standard criterion for the evaluation of population-based screening. The Wilson and Jungner principles are a guide for how governments make decisions about screening, but how they are put into practice varies around the world to fit the needs of local circumstances (*2,7*). The American College of Obstetricians and Gynecologists (ACOG) issued a committee opinion in 2017, with an expanded panel recommending screening for conditions with a carrier frequency above 1%. Guo *et al*. also found that screening only for conditions with carrier frequencies above 1%, corresponding to variants in just 40 genes in their study, would identify 76–97% of carrier pairs. Chokoshvili *et al*. compared 16 different suppliers of expanded carrier screening panels, and they discovered that only three diseases (Cystic Fibrosis (CF), Maple Syrup Urine Disease 1B and Niemann-Pick Disease) were found to be screened in common (*2,8*). Concerning the current status of carrier screening, the American College of Medical Genetics and Genomics (ACMG) published a practice resource in 2021 and proposed the establishment of a tier-based carrier screening system. This system is divided into four tiers, with Tier 1 screening focusing on screening for CF and Spinal Muscular Atrophy (SMA) regardless of ethnicity or population. Tier 2 and tier 3 screenings propose using carrier frequency as a way of selecting what to include in carrier screening in the general population. Tier 4, on the other hand, doesn't have a minimum frequency requirement, and the number of conditions that can be screened can be substantially expanded. The practice resource recommends Tier 3 carrier screening be offered to all patients who are pregnant or planning pregnancies, and Tier 4 screening be used when a family or personal medical history necessitates the test and when the pregnancy is the result of a known or potential consanguineous marriage (*2,6*) (Figure 2).

4. An approach to the current status of carrier screening policies in the selected countries

Diagram: COMPREHENSIVE CONTROL PROGRAM FOR RARE DISEASES

(DISEASES ONCET AND PROGNOSIS)

PRECLINIC PHASE		CLINIC PHASE	
PRIMORDIAL PREVENTION	**PRIMARY PREVENTION**	**SECONDARY PREVENTION**	**TERTIARY PREVENTION**
Evaluation of the social determinants	Determinations of the risk groups	Early diagnosis	Monitoring of patient and ongoing care
Legal regulations	Elimination of risk factors	Suitable treatments	Rehabilitation interventions
Making the infrastructure for health services	Premarital genetic screenings	Easy access to health services	Independency of the people and adequate income
Public education and raising the literacy level of the public	Prevent risk factors	Education of health personnel	Social participation
Raising the welfare level of the public	Prevent exposures	Easy-to-use healthcare facilities	

QUARTERNARY PREVENTION

Prevention the overmedicalization
Careful prescription/Attentive medical intervention/avoiding side effect
Patient safety/Health services safety
Avoiding fragmented and extreme specialization
Combination of palliative care and monitoring

Figure 1. Diagram illustrating comprehensive control program for rare diseases. This diagram is developed by Dr. Akdur (*2*).

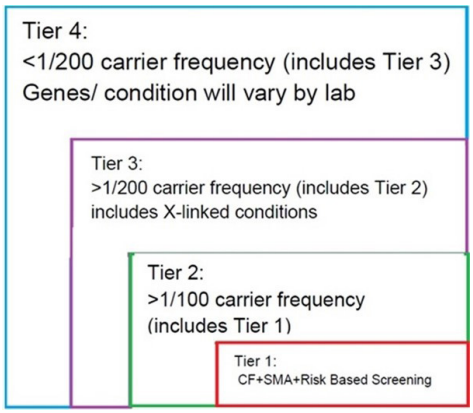

Figure 2. Diagram illustrating the tier based approach proposed by ACMG. This figure is based on the Tier Based Approach Proposed by ACMG (*6*).

In this review, databases, websites and organizations were examined with the purpose of examining the current literature on carrier screening. Additionally, the number of diseases/disorders screened by carrier screening in the United States, Canada, the United Kingdom, Israel, China, Australia, Italy, Germany, the Netherlands, and Turkey, the specific conditions under which these diseases/disorders are screened, and the official policies of these countries on carrier screening, including guidelines published by interested associations and organizations, were investigated. The official websites of the national health institutes and health ministries of these countries were analyzed.

4.1. The process of study selection and the strategy applied to obtain data

Databases such as PubMed, ResearchGate, and Google Scholar were searched with "((carrier screening [Title/Abstract]) or (carrier screening program [Title/Summary])) or ((preconception carrier screening [Title/Summary]) or (premarital screening [Title/Summary])" strategy with an emphasis on open access articles. "(("Country" carrier screening) or ("Country" carrier screening program))" search methods were adopted whilst websites, organizations and Google Search database, as well as the PubMed database, were studied. A total of 1,071 journal articles, books, and reports were scanned in the databases in addition to records from websites and organizations. Records published between 1972 and 2022 were examined, with an emphasis on the ones published in 2017 and later. The research began in October 2021 and was mainly conducted from July 2022 to November 2022. The study mostly utilized English-language sources, but it also examined documents in the national languages of Turkey, Italy and the Netherlands. The evaluation of the literature, data extraction and assessments were conducted collectively by the authors. The review was formatted based on the PRISMA guidelines (*9*).

4.2. Eligibility criteria and the assessment of risk of bias

The authors benefited from elimination criteria such as *i*) subject and terminology cooperation among obstetrics and gynecology and public health disciplines; *ii*) construction to the extent that it may benefit multiple specialties; *iii*) emphasis on reports written in English; and *iv*) attainment of coherence when the reports were analyzed for inclusion and exclusion. The risk of bias assessment was conducted with the ROBIS tool by the authors (*10*). Eligibility criteria, synthesis process, and findings were addressed. Additionally, the criteria for identifying and collecting the studies to be included in the paper were investigated.

5. Current status of carrier screening policies in selected countries based on the number of diseases/conditions screened and the spesific circumstances the diseases/conditions screened

A total of 32,662 records from 4 databases, 516 records from websites, and 464 records from organizations were identified with search engines. Subsequent to retrievals and assessments, 41 reports were included in the review (Figure 3)

In this review, the diseases/disorders screened for or recommended to be screened by the official carrier screening programs of the ten countries were described. The conditions under which these diseases were screened were included by searching publicly available sources on the internet, including databases, websites, and organizations. However, different types of resources have been publicly accessible for each country. Since there haven't been routinely created resources for rare diseases, the most recent and available materials were utilized in order to emphasize rare diseases. To address the issue, the documents were classified and prioritized according to this classification. The following documents were prioritized by the authors: government data, committee guideline data, pilot study data, and national institution data, respectively. The data obtained is presented as a table consisting of 73 diseases/disorders. A coding system was generated by the authors to demonstrate the data since the carrier screening plans of each country vary significantly. The coding system, consisting of numerals and letters, was explained in detail below the table. The codes "A, A1, A2, B, C, C1, C2, C3, C4, D, E" symbolize the conditions for which diseases are screened. The codes "cg, gd, ps, ni" are the abbreviations of the following document types: committee guideline data, government data, pilot study data, and national institution data, respectively. The codes "cg1, cg2, gd1, gd2, gd3, gd4, ps, ni1, ni2, x1" categorize and represent the data resources of each country (Table 1, Online Data, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=165*).

The availability of different types of data

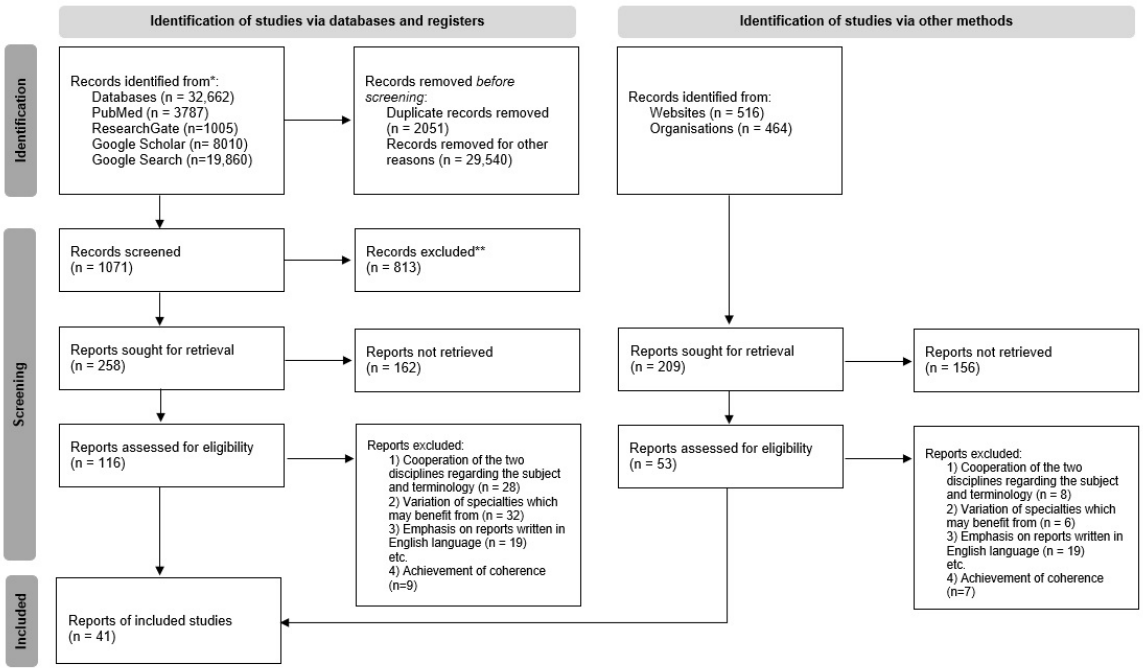

Figure 3. Diagram illustrating the identification of records. This diagram is developed based on PRISMA 2020 (*9*). The criterion of the two disciplines were formulated on obstetrics and gynecology and public health disciplines.

demonstrates the significance and implementation of carrier screening programs in various countries. However, a homogeneous comparison cannot be made between the carrier screening programs of the countries due to different data. In terms of application, government data and committee guideline data take precedence; however, it is not possible to rank the other forms of data.

The number of diseases/disorders screened by the ten countries ranged from 3 to hundreds. It is recommended to screen for 18 diseases/disorders in the USA (*11*) and 16 diseases/disorders in Canada (*12*) according to committee guidelines. 4 diseases/disorders in the UK (*8*), 30 diseases/disorders in Israel (*13,14*), and 3 diseases/disorders in Turkey (*15-17*) are screened for based on government resources. In Italy, 3 diseases/disorders are recommended to be screened by molecular genetic testing by the government resources (*18,19*). In the Netherlands, 47 diseases/disorders may be screened in a national health institute (*20*). In Australia, it is recommended to screen the general public for 3 diseases/disorders even though it is possible to screen for hundreds of diseases/disorders in a national health institute (*21-23*). 11 diseases were screened in a pilot study in China in 2019 (*24*). Although there are laboratories in Germany that are able to screen for numerous conditions, social screening is not currently available (*25*). Carrier screening programs were provided free of charge or for a fee by the government in some countries and for a fee by private health institutions in others. The carrier screening test is not covered by the government in the USA (*26*), Australia (*22*), Germany (*25*), or the Netherlands (*27*); however, private health insurance is accessible. Under specific conditions, such as being referred by a hospital specialist, having designated ethnic origins, and marriage, screening is covered by health insurance in the UK (*28*), Israel (*13*), and Turkey (*15,16*), respectively. While screening tests for some diseases/disorders were conducted nationwide, tests for other diseases/disorders were administered to at-risk groups identified by different countries based on their own populations (*8,11-18,20-24*). Compared to newborn screening (NBS), carrier screening programs revealed a higher degree of heterogeneity in terms of the diseases/disorders screened for, the number of diseases/disorders screened for, and the groups screened for, and the tests were generally not covered by the state or only a small number of diseases/disorders were covered by the state (*29*).

6. Carrier screening in Turkey

The carrier screening program in Turkey is available as the Premarital Screening Program, which consists of the Premarital Hemoglobinapathy Screening Program and the Premarital Carrier Screening Program for SMA.

6.1. Premarital screening program in Turkey

Anamnesis, physical examinations, and blood sampling for laboratory tests are administered to couples who are getting married. The program includes tests for hemoglobinopathy screening, blood group determination, SMA screening, and infectious disease screening (*16,30*).

6.2. Premarital hemoglobinopathy screening program in Turkey

The prevalence of beta-thalassemia carriers in the Turkish population is 2.1%, with regional variations ranging from 0.6% to 13%. In the absence of any intervention program, it is estimated that 400 new cases arise each year (*17*). Studies also revealed that Turkey has an alpha-thalassemia prevalence of 0.25%, with regional variations (*31*). Although the Law on Combating Inherited Blood Diseases was published in 1993 and the Regulation on Hemoglobinopathy Control Program and Diagnosis and Treatment Centers was published in 2002, thalassemia has not been eradicated in Turkey in 25 years. Thalassemia is still considered to be a condition that has a severe burden on the Turkish economy (*30*). The program aims to extend the life expectancy of existing hemoglobinopathy patients, increase their quality of life, and prevent abnormal hemoglobin diseases (*15*). The operation of Premarital Hemoglobinopathy Screening Program in Turkey was reported in Figure 4.

6.3. Premarital carrier screening program for SMA

Due to Turkey's significantly high carrier rates, the SMA carrier screening program began to be implemented in 81 provinces as of the end of December 2021. This initiative aims to identify couples who are both SMA carriers, give genetic counseling to families, inform and guide individuals about prenatal or pre-implantation diagnostic test choices, and reduce the long-term morbidity and mortality associated with SMA disease. SMA carrier screening is administered to spouses who apply for a premarital health evaluation and to married couples (*16*).

7. Importance of screening in consanguineous marriages

In clinical genetics, consanguineous marriages are defined as marriages between second cousins (fifth degree relatives) or more closely related family members (*32*). A study published in 1972 reported that the rate of consanguineous marriages in Turkey was 29.2%, and 80% of these marriages were between children

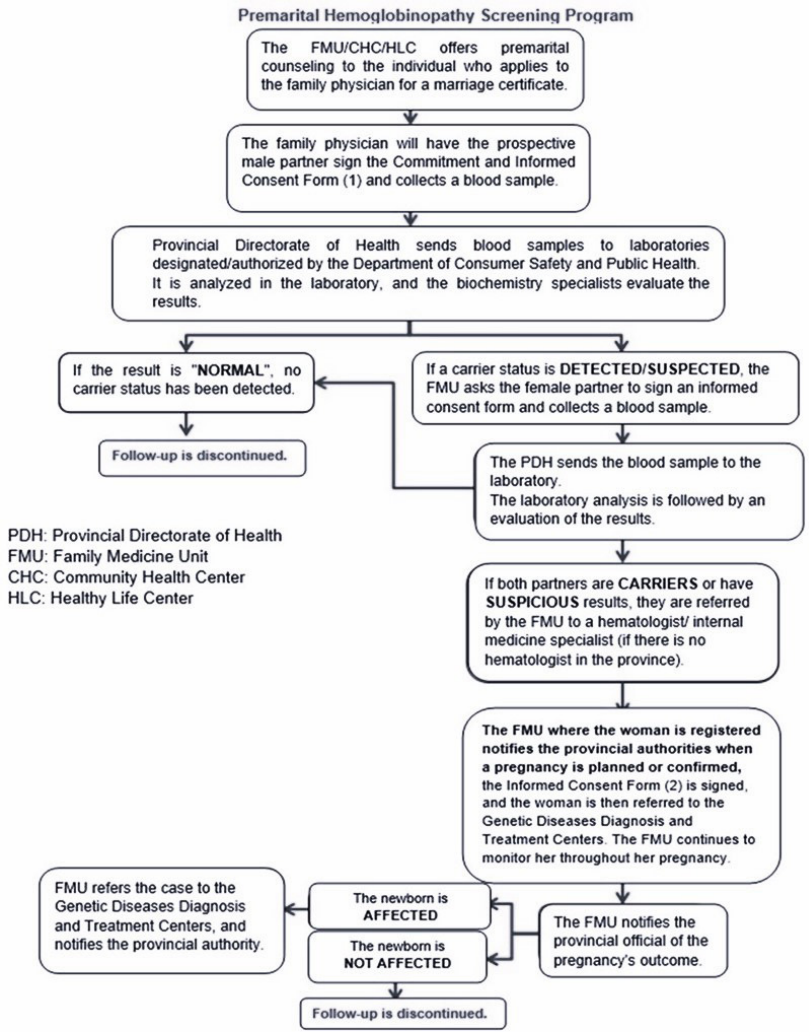

Figure 4. Diagram illustrating the operation of the Turkish premarital hemoglobinopathy screening program. This diagram is based on the Premarital Hemoglobinopathy Screening Program of the Republic of Turkey, Ministry of Health (*17*).

of siblings (*33*). Moreover, according to data from the Turkish Statistical Institute (TÜİK), 8.3% of the population were married to their first cousins in 2021 (*34*). The reproductive risk that sets consanguineous couples apart from other couples in the general population is reportedly related with AR diseases/ disorders, according to a 2021 study looking into the impacts of consanguineous marriages. A protocol based on whole exome analysis (WES) was developed, where the exomes of 39 consanguineous couples were studied, by the researchers in response to this statement. It was reported that eight couples shared heterozygosity for at least two pathogenic mutations, whereas 53.8% of couples shared heterozygosity for at least one variant that was thought to be pathogenic or possibly pathogenic for an AR disease. It was recommended that carrier screening with WES should be incorporated into genetic counseling for all consanguineous couples and since consanguineous couples occasionally have more than one shared pathogenic gene, even couples whose children have already been diagnosed with AR disease should undergo carrier screening with WES (*35*). In a different study, preconception carrier screening (PCS) was carried out on a population of Dutch women of Turkish and Moroccan descent in 2018, where the rate of consanguineous marriages in these groups was reported to be around 20–25%. Although already known to have a high incidence of AR diseases in their families, after the screening results were disclosed, they did not accept the reproductive options of prenatal genetic diagnosis (PND), pregnancy termination (TOP), *in vitro* fertilization (IVF) with donor oocytes, artificial insemination with sperm donation (AID), or adoption. IVF with preimplantation genetic diagnosis (PGD) was, on the other hand, widely accepted. The study also noted that women were vocal about avoiding getting married or even divorcing when both partners were carriers and favored PCS for premarital screening. In order to provide successful health care, it was claimed that bringing attention to consanguineous marriages and their effects, as well as being sensitive when giving information, screening, and counseling services to these families, were essential (*32*).

8. Advantages and disadvantages of carrier screening

The advantages of universal screening include the elimination of ethnic or racial factors, the reduction of stigma, and the removal of the burden on patients or physicians to recognize risk (*2,8*). For a screening program to remain as a beneficial source, however, long-term assessments must be made, and its application to the current context and conditions, its technological applicability, and the efficacy of the treatment that follows must also be taken into account. For instance, the impact of a nationwide CF carrier screening program in Israel reduced the number of infants born with CF who have a relatively severe phenotype. As a result, the program's organizers chose to remove CF from the NBS panel. When offered during the preconception period, carrier screening allows couples to make informed reproductive decisions, such as not having children, adopting, using PGD or IVF to avoid having an affected child, or having a child naturally while being aware of the risks. By providing prospective parents with a diagnosis before the baby is born, pre-conception screening can prevent the birth of an affected child. Attempting to prevent the decision to terminate an affected pregnancy makes it more favorable in this regard than prenatal screening (*2,7*).

Universal screening is expected to increase costs and complicate genetic variant analysis across laboratories. There will be a need to ensure that carrier screening tests have adequate accuracy and sensitivity across the population (*2,8*). The expansion of carrier screening panels, in contrast to NBS public health programs, is currently primarily driven by commercial interests, is not founded on professional guidelines or defined criteria, and leads to a wide selection of tests covering hundreds of conditions. It may appear appealing to use a single test for multiple diseases/disorders at nearly the same cost. However, Next Generation Sequencing (NGS) may inadvertently begin to include diseases/disorders that are mostly symptomatic in adults, less pathogenic DNA variants or variants of unknown significance. Also, not all prospective parents choose to participate in carrier screening tests or act on screening results because screening tests are not always able to detect all carriers. ACOG has stated that NBS remains significant as a screening method and cannot be substituted for this reason (*2,36*).

9. Public perspectives

In recent years, numerous studies have been conducted on diverse populations throughout the world with the objective of assessing public readiness and perspective on the subject of carrier screening, with a focus on issues including test providers, availability, suitable planning, and disclosure of the results, follow-up care, the hesitations and willingness of the people, and in what forms they should be expected to comply with these programs.

In 2018, Mathijssen *et al.* examined 182 participants' pre- and post-carrier screening experiences with the PCS offer for 4 AR illnesses in the Netherlands. It was mentioned that genetic conditions were publicly acknowledged among the participants, and they had been told about the screening *via* their families and coworkers. It was stated that 63% of participants reported feeling apprehensive while awaiting their screening results, but their anxiety levels subsided subsequently, and only a small percentage of carriers reported feeling less healthy. It was also notified that 97% of those tested reported no regrets regarding the test, and 97% would suggest it to

others. Additionally, the readers were informed that 94% of respondents agreed that couples should always seek pre-test counseling, and 83% stated they should seek it from a genetic counselor rather than their physician (*37*).

In a 2021 study by Bonneau *et al.* in France, it was shown that 91% of 1,568 participants had a favorable opinion of PCS, and 57% would be open to screening if it were available. A family doctor's or a gynecologist's medical prescription and social security insurance coverage for the test were reported to be the best ways to recommend testing, according to the majority of responders. Because of their ethical or moral convictions and concern that the results would cast doubt on the pregnancy, 19% of respondents claimed they were unwilling to be tested in the study. Despite the possibility that the results could medicalize the pregnancy, the majority of respondents viewed the test as a medical advancement. According to the findings, 65% of French physicians were not aware of this kind of test, and there was no discernible knowledge gap between them and the other respondents (*38*).

In a 2020 study conducted in the UK by Boardman *et al.*, the experiences and perspectives of a group of 20 thalassemia patients, those who have family members with thalassemia, and thalassemia carriers about preconception, prenatal, and neonatal thalassemia screening were examined. All prospective screening modalities were reported to receive a lot of encouragement because the majority of participants described thalassemia as a burdensome condition with a variety of adverse effects. However, particularly in religious communities, it was discovered that cultural, social, and, to a smaller degree, religious factors devalued the advantages of early screening, as stated by the study (*39*).

In 2021, Rabkina *et al.* surveyed 260 women who were nulliparous. 43.5% of respondents indicated that they were aware of carrier screening prior to the poll, and 77.8% indicated that they were interested in it. Reassurance and the desire to have information while making decisions about future pregnancies were listed as the key drivers of interest. A healthcare professional's in-person consultation was preferred (*40*).

Participants in a 2017 study by Chokoshvili *et al.* in Belgium were reported to show strong interest in reproductive genetic testing, such as prenatal testing and carrier screening for AR diseases/disorders, but low interest in genetic testing of newborns for susceptibility to adult-onset diseases/disorders. In addition, it was mentioned that there was a greater desire to undergo a predictive genetic test on oneself when the genetic testing is limited to ailments that are treatable or avoidable. According to the study, the vast majority of respondents stated that commercial offers of genetic testing through pharmacies or the internet were inappropriate and that genetic tests should instead be carried out in hospitals with a doctor's approval (*41*).

Carrier screening programs for rare diseases, like other diseases, are the result of a collaborative effort between multiple medical disciplines. In the existing literature, however, there are few studies that incorporate the views of many fields. There is also limited literature on carrier screening programs for rare diseases, as well as access to a representative sample of relevant government papers. It may be advantageous to identify the most effective carrier screening techniques for the needs of the countries, because the diseases expected to be seen may differ accordingly. These screenings should be in accordance with their national health policies and implemented as routine programs by conducting cost analyses along with the potential screening outcomes. All countries' genetic infrastructures should be thoroughly studied, and appropriate planning should be made by health professionals for diseases/disorders that can be detected through carrier screening, which can cause workforce loss, disease disability, and death, which may influence future generations in terms of public health, or whose disease outcomes might be disastrous and economically destructive and should be implemented as routine programs. Therefore, it is expected that carrier screening programs, similar to newborn blood spot screening, will become more widespread and that the examples of many countries will serve as a model for other countries in these efforts to protect public health (*29*).

10. Conclusion

In conclusion, this study has shed light on the disparities in carrier screening programs across countries, emphasizing the significant policy differences that exist. These variations, ranging from the involvement of health ministries to committee guidelines, university-level research, pilot studies, and individual scientists' research, underscore the low global priority and insufficient attention given to rare diseases.

Moving forward, further research should focus on establishing the necessary scientific infrastructure to develop and implement universal carrier screening programs. This effort is crucial for addressing inequalities in both local and global contexts, as health is a fundamental human right that should be ensured from birth. While common causes of mortality and morbidity such as chronic diseases and accidents receive considerable attention, rare diseases have a profound impact on individuals and society. They cause illness, disability, and death, leading to the loss of productivity, economic burdens, and psychological issues.

Rare diseases contribute significantly to the disease burden in terms of years lost due to premature death (YLL) and years lost due to disability (YLD). Neglecting rare diseases can result in severe healthcare challenges, especially in small-local communities. Therefore, it is imperative to define diagnosis, treatment, and

rehabilitation services for these diseases and address the social, psychological, and economic burden on caregivers in countries without carrier screening programs. For countries with existing programs, conducting a comparative cost analysis is necessary to allocate financial resources for individuals with the disease who were not screened and may have children.

Considering the high costs associated with diagnosing and treating rare diseases, it is crucial for international organizations to provide financial support to countries lacking sufficient economic infrastructure. By establishing and implementing carrier screening programs, the occurrence of diseases can be prevented, leading to improved health and overall societal well-being in future generations.

While this study serves as a guide for developing countries, it is essential to acknowledge that rare diseases pose a more severe challenge in underdeveloped regions where health problems often go undetected and health records are inadequate. However, rare diseases will not be noticeable until common mortality causes such as hunger, poverty, and acute infections are eliminated. Despite this study and other studies, rare diseases will continue to be the invisible face of the iceberg due to the nature of development differences between countries.

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