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THE TWO ESSENTIAL COMPONENTS OF A COMPREHENSIVE RARE DISEASE CONTROL PROGRAM

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Summary

Rare diseases, which affect a small percentage of the population and have a negative impact on personal well-being, also affect millions of people globally and are recognized as an important public health problem. Due to the devastating nature of rare diseases, they have significant negative economic, social, and psychological impacts on patients and their communities, as well as challenging and costly diagnostic and treatment processes. The current ability of society to control common diseases has led to the rise of rare disease control as an important issue on the public health agenda. The two essential components of a comprehensive rare disease control program are: 1) primary prevention with carrier screening and 2) secondary prevention with early detection screening. Given the different genetic structures of nations and insufficient data on rare diseases, İt may be considered advantageous to study the genetic infrastructures of countries, analyze cost-effectiveness along with the potential screening outcomes in accordance with national health policies, and identify the most effective carrier screening techniques. It is recommended to establish international criteria to ensure the affordability and effectiveness of carrier screening programs for the protection of public health, to model examples of countries with active and regular carrier screening programs similar to newborn blood spot screening, and to expand carrier screening programs.

Keywords: rare diseases prevention, carrier screening, preconception carrier screening, premarital screening, early diagnosis screening

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 a rare disease [1]. While the European Union defines rare diseases as life-threatening or chronically debilitating diseases that affect no more than 5 in 10,000 individuals, the Orphan Drug Act of 1983 and the Rare Diseases Act of 2002 define rare diseases as diseases that affect fewer than 200,000 individuals or affect 1 in 1500 individuals in the United States [1,2]. Data on the causes, pathophysiology, semiology, epidemiology, and natural history of rare diseases are limited [3]. The diagnosis and treatment of rare diseases, which are recognized as a serious health problem worldwide, are very challenging and costly [3,4]. As with all diseases, in order to be successful in controlling rare diseases, the health program to be implemented must be based on protection and prevention. Therefore, it is very important

to establish a comprehensive service network that includes the whole community and all its services to combat rare diseases.

The significance of health screenings in rare diseases

Health screenings are programs that are applied to healthy people at regular intervals [5]. The primary goals of screening programs are as follows: 1) Identifying at-risk individuals or carriers for screening, protecting them from the risk, and preventing disease onset (primary prevention). 2) Detecting and efficiently treating affected individuals at an early stage (at the asymptomatic/ preclinical stage) (secondary prevention).

Screening is used in rare disease control programs for two purposes: 1) identifying individuals who are carriers (autosomal recessive (AR) or heterozygous for a pathogenic or possible pathogenic variant in an X-linked disease [6]; in other words, those who are at risk of marrying or having children (primary prevention); and 2) ensuring that affected individuals are diagnosed at an early stage and receive the most appropriate and effective treatment.

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2) ensuring that affected individuals are diagnosed at an early stage and receive the most appropriate and effective treatment.

As seen in the diagram below, preventive health services are classified into five groups/classes. These groups are named primordial, primary, secondary, tertiary, and quaternary prevention. These groups also apply to rare diseases. In this context, the use of screening tests in a comprehensive rare disease control program is the most important tool or intervention. (Diagram: Comprehensive Control Program for Rare Diseases

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

This diagram is developed by Dr. Akdur

Who is screened and who should be screened?

Approximately 1 in 100 couples worldwide are at risk of having an affected child because of the possibility that one or both individuals may be recessive carriers [8]. The term carrier specifically refers to individuals who are heterozygous for a pathogenic or potentially pathogenic variant in an AR or X-linked disease/disorder [6]. Because carrier status does not usually affect one's own health, the birth of an affected child is typically unexpected [8].

Carrier screening, there can detect the presence of these a blood sample or other biological material. Over 40 years ago, Wilson and Jungner, on behalf of the World Health Organization (WHO), developed a gold standard criteria for the evaluation of population-based These screening pioneers have proposed evaluating grounds in a way that explores four themes: the screened condition, the test, the treatment, and the screening program. While the Wilson and Jungner point of reference for government decision-making on screening, their practical implementation varies around the world to best adapt to local circumstances [9].

It is estimated that 1-2% of couples have a high probability of having a child with an AR or X-linked genetic disease. Often, people are unaware of genetic risks before having a child and discover their carrier status only after an affected is born. Carrier screening informs couples about their genetic risk prior to or during pregnancy. Couples at high risk can either plan for an affected child or choose reproductive procedures to avoid having one [10].

Advantages 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 [11]. 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 considered. For instance, preconception carrier screening for Spinal Muscular Atrophy (SMA) could no longer be required if a SMA medication can effectively treat newborns at an affordable cost and is incorporated in newborn screening (NBS). The impact of a nationwide Cystic Fibrosis (CF) carrier screening program in Israel has reduced the number of infants born with CF who have a relatively milder phenotype. As a result, the program's organizers have chosen to remove CF from the NBS panel. However, when a disorder has a treatment that worsens its effects on society, particularly economically, it can burden society and make preconception carrier screening even more critical [8]. When offered during the preconception period, carrier screening allows couples to make informed reproductive decisions, such as not having children, adopting, using Preimplantation Genetic Diagnosis (PGD) or In Vitro Fertilization (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 [9].

Disadvantages of Carrier Screening

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 [11]. 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, but if the risks and benefits are not carefully weighed, the program may inadvertently begin to include diseases/disorders that are mostly symptomatic in adults or variants of unknown significance. Another potential disadvantage of applying Next Generation Sequencing (NGS) in screening is the identification of less pathogenic DNA variants or variants of unknown significance. Also, the advantages of early treatment are unclear. Furthermore, American College of Obstetricians and Gynecologists (ACOG) has stated that NBS cannot substitute for carrier screening and that NBS does not decrease the potential advantages of carrier screening. NBS remains significant. 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 [8].

The Perspective of Genetic Science

When carrier screening is mentioned, the perspective of genetic studies should be emphasized since screening strongly depends on the innovations the discipline brings. The aim of genetic screening tests is to guide couples to make autonomous, informed choices [12]. Technological advances have allowed more conditions to be detected, as panels spanning multiple conditions simultaneously replaced the gene-by-gene evaluation, and they have allowed carrier screening to become universal instead of a procedure specific to high-risk populations, making genetic tests affordable [11,13].

Whole Exome Sequencing (WES)

WES has been recognized as an ideal carrier screening method. Considering the technical advances of carrier screening and the application of a technological advance like WES, it is important to understand that WES does not identify every genetic variant that an individual carries. Among the cases where WES fails to identify a pathogenic variant, the following can be highlighted: mutations through deletion or duplication of all or part of the gene; microsatellite expansion mutations (dynamic mutations), diseases/disorders associated with mutations in two different genes (digenic inheritance), mutations not located in an exon (e.g., a pathogenic mutation in a promoter or intronic region), mutations in genes whose exons are captured with low efficiency by existing exonic selection kits; mutations in a gene that is very similar to other genes (paralogs) in the human genome, and mutations caused by the addition of a substitutive element [14].

Sequencing and Expanded Screening in Carrier Screening

Following the mentioned advances, it must also be noted that the identification of sequence variations in numerous genes concurrently at a low cost is made possible by next-generation sequencing. Carrier screening relies on next-generation sequencing (NGS), polymerase chain reaction (PCR), Sanger sequencing, multiplex ligation-linked probe

amplification (MLPA), microarray and other laboratory methods to identify large-scale structural variants (SVs), including single nucleotide variants (SNVs) and copy number variants (CNVs) to identify small-scale genetic alterations. It is necessary to establish carrier screening procedures in a way that provides individuals an equal opportunity to learn about their reproductive risk using next-generation sequencing technology since expanded carrier screening is not expression specific. A better comprehension of this risk can enable patients to make informed reproductive decisions. Reproductive choice is a recognized indicator of the clinical value of universal carrier screening [6].

The Importance of Variants of Undetermined Significance (VUS) in Screening Reports

Typically, laboratories only report variations that are identified as pathogenic (>99% certainty) or likely (>90% certainty) pathogenic in a screening environment. However, there are cases where a variant of unknown significance (VUS) is reported [6]. Expanded Carrier Screening (ECS) reports currently include only pathogenic or likely pathogenic variants (P/LPVs) while VUS are not reported. P/LP and VUS carriers are thought to be at risk, especially for genes with high P/LP carrier rates. Researchers examined the consequences of VUS in an Ashkenazi Jewish population in a 2020 study, and they reported that in about detect P/LP and VUS carriers. According to the study's findings, if VUS are reported, the yield of ECS might be increased, and detection rates for couples at risk would dramatically increase [15]. This could involve recommending that a VUS be considered for reporting if, for example, one member in a couple is known to be carrying a pathogenic or potentially pathogenic variant after the second partner has been screened [6]. Regardless of the report's contents, patients must be made aware that the interpretation of clinical genetic test results is susceptible to change, that additional treatment may be required, and that while a negative screening result reduces the risk of carrying the diseases/disorders screened for, it does not completely eliminate it. The risk of being a carrier of any disease/disorder is never zero [15].

Genetics and Public Health

Public health aims to evaluate the redesign of diagnostic and laboratory services to integrate new genome-based technologies [16]. In order to implement carrier screening, it is necessary to ascertain the most effective approach for integrating genomic applications in population health. The implementation gap and health inequities may be reduced by collaboration between healthcare organizations and public health disparities [17].

Ethical Perspective

It may be considered beneficial to tackle ethical issues referring to carrier screening. Regarding the population- based screening aspect, the American College of Medical Genetics and Genomics (ACMG) noted that the accessibility of reproductive alternatives may vary depending on a number of social, legal, and cultural factors in various regions. It has been seen that partners are frequently chosen not at random but rather in response to social pressures, norms, and expectations [6]. Individuals may have different opinions on what is acceptable to screen for. Furthermore, routine carrier screening may cause new societal pressure on individuals to make particular choices [11]. An option that is rather important to mention is pregnancy termination, in other words, therapeutic abortion [8].

Even though some groups argue that abortion of an affected fetus during the prenatal period should not be recognized as a treatment option, ACMG has stated that when a fetus is diagnosed with a genetic disorder or congenital anomaly, couples should have the option of terminating the pregnancy [8,18].

Conclusion and Recommendations

Rare diseases create devastating effects by causing illness, disability and death when analyzed from the perspective of the individual, while from a social perspective, they have detrimental impacts on patients with rare diseases and their surroundings, including loss of workforce, economic, social, and psychological issues for both the sufferer and the care provider.

The loss of life at a young age of individuals with rare diseases should be seen as an important preventable cause of disease burden in terms of years lost due to death at a young age (YLL) and years lost due to disability (YLD).

All countries should establish comprehensive community and preventive service-based health programs to control rare diseases.

International criteria should be established to ensure the affordability and effectiveness of screening programs.

The genetic structures of countries should be thoroughly studied and appropriate planning to implement and expand the scope of carrier screening should be done by health professionals in accordance with the national health policies of the countries.

Intersectoral cooperation should be ensured in the devising and implementation of carrier screening.

A publicly-funded approach is essential to ensure that carrier screening is truly universal and equitable.

Researchers should include studies and advancements referring to genetic sciences, as well as the public's perspective on carrier screening, genetic testing and rare diseases in future studies.

Keywords: rare diseases prevention, carrier screening, preconception carrier screening, premarital screening, early diagnosis screening

References

1. Julkowska, D., Austin, C. P., Cutillo, C. M., Gancberg, D., Hager, C., Halftermeyer, J., Jonker, A. H., Lau, L. P. L., Norstedt, I., Rath, A., Schuster, R., Simelyte, E., & van Weely, S. (2017). The importance of international collaboration for rare diseases research: A European perspective. In Gene Therapy (Vol. 24, Issue 9, pp. 562–571). Nature Publishing Group. https://doi.org/10.1038/gt.2017.29

2. Taruscio, D., Capozzoli, F., & Frank, C. (2011). Rare diseases and orphan drugs. Ann Ist Super Sanità , 47(1), 83–93.

3. de Vrueh, R., Baekelandt, E. R. F., & de Haan, J. M. H. (2013). Background paper 6.19 rare diseases.

4. Orphan Products: Hope for People With Rare Diseases | FDA. (n.d.). Retrieved October 1, 2022, from https://www.fda.gov/drugs/ information-consumers-and-patients-drugs/ orphan-products-hope-people-rare-diseases

5. Akın, H., Aşıkovalı, S., Aykut, A., Bahsi, T., Başaran, S., Bolat, H., Bora, E., Bozkurt, G., Çağlayan, A. O., Çobanoğlu, N., Durmaz, A., Durmaz, B., Erdem, H. B., Ergün, M. A., Güleç, Ç., Karaca, E., Karakaya, T., Mıhçı, E., Öz, Ö., & Ünsel, M. (2020). Güncel genetik tabanlı tarama testleri (H. Akın, Ed.; 1st ed.).

6. Gregg, A. R., Aarabi, M., Klugman, S., Leach, N. T., Bashford, M. T., Goldwaser, T., Chen, E., Sparks, T. N., Reddi, H. v., Rajkovic, A., & Dungan, J. S. (2021). Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine, 23(10), 1793–1806. https://doi. org/10.1038/S41436-021-01203-Z/ATTACHMENT/BE6DEE31-3AC2-45A3-9148-FC510C4C8F5D/MMC1.PDF

7. Fidan, C., Orun, H., Alper, A. B., Unver, C. N., Sahin, O. C., Ugurlu, Z., Akdur, R., & Taruscio, D. (2022). Expanded newborn bloodspot screening: developed country examples and what can be done in Turkey. Intractable & Rare Diseases Research, 11(2), 63. https://doi. org/10.5582/IRDR.2022.01039

8. Cornel, M. C., Rigter, T., Jansen, M. E., & Henneman, L. (2021). Neonatal and carrier screening for rare diseases: how innovation challenges screening criteria worldwide. Journal of Community Genetics, 12(2), 257–265. https://doi.org/10.1007/S12687-020-00488-Y/TABLES/2

9. Molster, C. M., Lister, K., Metternick-Jones, S., Baynam, G., Clarke, A. J., Straub, V., Dawkins, H. J. S., & Laing, N. (2017). Outcomes of an international workshop on preconception expanded carrier screening: Some considerations for governments. Frontiers in Public Health, 5(FEB), 25. https://doi.org/10.3389/ FPUBH.2017.00025/ BIBTEX

10. Victorian Clinical Genetics Services. (2019). Reproductive genetic carrier screening - is more better? The Partumpost, 3(3).

11. Rowe, C. A., & Wright, C. F. (2020). Expanded universal carrier screening and its implementation within a publicly funded healthcare service. Journal of Community Genetics, 11(1), 21–38. https://doi.org/10.1007/S12687-019-00443-6/TABLES/8

12. Singer, A., & Sagi-Dain, L. (2020). Impact of a national genetic carrier-screening program for reproductive purposes. Acta Obstetricia et Gynecologica Scandinavica, 99(6), 802–808. https://doi.org/10.1111/AOGS.13858

13. Bajaj, K., & Gross, S. J. (2014). Carrier Screening: Past, Present, and Future. Journal of Clinical Medicine, 3(3), 1033. https://doi. org/10.3390/JCM3031033

14. Santos, C. M. de A. dos, Heller, A. H., Pena, H. B., & Pena, S. D. J. (2021). A Protocol for Preconceptional Screening of Consanguineous Couples Using Whole Exome Sequencing. Frontiers in Genetics, 12. https://doi.org/10.3389/FGENE.2021.685123

15. Fridman, H., Behar, D. M., Carmi, S., & Levy-Lahad, E. (2020). Preconception carrier screening yield: effect of variants of unknown significance in partners of carriers with

clinically significant variants. Genetics in Medicine, 22(3), 646–653. https://doi.org/10.1038/ s41436-019-0676-x

16. Molster, C. M., Bowman, F. L., Bilkey, G. A., Cho, A. S., Burns, B. L., Nowak, K. J., & Dawkins, H. J. S. (2018). The evolution of public health genomics: Exploring its past, present, and future. Frontiers in Public Health, 6, 247. https://doi.org/10.3389/FPUBH.2018.00247/ BIBTEX

17. Khoury, M. J., & Holt, K. E. (2021). The impact of genomics on precision public health: beyond the pandemic. Genome Medicine, 13(1), 1–4. https://doi.org/10.1186/S13073-021-00886-Y/METRICS

18. ACMG Board of Directors. (2013). ACMG statement on access to reproductive options after prenatal diagnosis. Genetics in Medicine, 15(11), 900. https://doi.org/10.1038/gim.2013.139