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DEVELOPMENT OF AN ALGORITHM FOR DETERMINING OF GENETIC RISK AT THE PRIMARY HEALTHCARE LEVEL – A NEW TOOL FOR PRIMARY PREVENTION: A STUDY PROTOCOL

RAZVOJ ALGORITMA ZA DOLOČANJE GENETSKEGA TVEGANJA NA PRIMARNI RAVNI ZDRAVSTVENEGA VARSTVA – NOVO ORODJE V PRIMARNI PREVENTIVI: PREDSTAVITEV PROTOKOLA RAZISKAVE

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ABSTRACT

Introduction: Family history (FH) is an important part of the patients' medical history during preventive management at model family medicine practices (MFMP). It currently includes a one (or two) generational inquiry, predominately in terms of cardiovascular diseases, arterial hypertension, and diabetes, but not of other diseases with a probable genetic aetiology. Beside family history, no application-based algorithm is available to determine the risk level for specific chronic diseases in Slovenia.

Methods: A web application-based algorithm aimed at determining the risk level for selected monogenic and polygenic diseases will be developed. The data will be collected in MFMP; approximately 40 overall with a sample including healthy preventive examination attendees (approximately 1,000). Demographic data, a three-generational FH, a medical history of acquired and congenital risk factors for the selected diseases, and other important clinical factors will be documented.

Results: The results will be validated by a clinical genetic approach based on family pedigrees and the next-generation genetic sequencing method. After the risk of genetic diseases in the Slovenian population has been determined, clinical pathways for acting according to the assessed risk level will be prepared.

Conclusion: By means of a public health tool providing an assessment of family predisposition, a contribution to the effective identification of people at increased risk of the selected monogenic and polygenic diseases is expected, lessening a significant public health burden.

Keywords:
family medicine, pedigree, family history, genetic predisposition, population at risk

IZVLEČEK

Izhodišča: *Med obravnavo bolnikov v ambulanti družinske medicine (ADM) je družinska anamneza (DA) pomemben del bolnikove zdravstvene anamneze. Trenutno vsebuje poizvedbo predvsem o boleznih s kompleksno genetsko etiologijo (npr. kardiovaskularnih boleznih, arterijski hipertenziji in diabetesu). Genetski podatki ali DA o redkih boleznih niso vključeni. Zdravniki v Sloveniji poleg družinske anamneze nimajo na voljo pripomočka za določanje genetskega tveganja za kronične bolezni.*

Metode: *Razvito bo spletno orodje za določanje ravni tveganja za določene monogenske in poligenske bolezni. V presečno raziskavo bodo s pomočjo namenskega vzorčenja prostovoljno vključene ADM (N = 40), ki bodo zbirale podatke med zdravimi udeleženci preventivnih pregledov (n = 1200). Vsaka ADM naj bi vključila 30 zaporednih pregledovancev. Vključitveni kriteriji bodo odsotnost kroničnih bolezni, starost med 30 in 65 let ter soglasje za sodelovanje v raziskavi, izključitveni kriteriji pa starost pod 30 ali nad 65 let in nesposobnost sodelovati v raziskavi (slepota, psiho-organska prizadetost, duševna manjrazvitost). Zbirali se bodo demografski podatki, trigeneracijska DA, osebna anamneza prirojenih in pridobljenih dejavnikov tveganja ter pomembni klinični dejavniki za izbrane bolezni, vključno s srčno-žilnimi boleznimi, hipertenzijo, diabetesom, rakom, nevrološkimi, duševnimi, senzornimi in za druge v družini prisotne bolezni z možno genetsko etiologijo. Pri pregledovancih se bodo med preventivnim pregledom zbirali podatki o prirojenem in pridobljenem tveganju za omenjene izbrane bolezni iz osebne anamneze, prehranska anamneza, podatki o telesni aktivnosti, kajenju, pitju alkohola (AUDIT-C questionnaire), zaznavanju stresa, znakih depresije (tri presejalna vprašanja za depresijo), socialnih determinantah zdravja, indeksu telesne mase, krvnem tlaku, laboratorijskih vrednostih (krvni sladkor, lipidogram) in izračunu srčno-žilnega tveganja.*

Ključne besede:
družinska medicina, rodovniki, družinska anamneza, genetska predispozicija, tveganju izpostavljena populacija

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1 INTRODUCTION

In family medicine (FM), family history (FH) has been a crucial part of patient management for centuries. Taking an FH provides insight into a patient's family background and helps to clarify the context of their problems (1), while offering data on genetic predisposition and reflecting interactions between genetic, environmental, cultural and lifestyle characteristics.

Traditionally, the taking of an FH focuses on symptomatic patients in order to find a possible family predisposition for a specific disease. The modern approach is to establish genetic risks for specific diseases in healthy people (1). A positive FH is crucial in determining the risk of monogenic disorders – diseases associated with mutation in a single gene. The rare monogenic diseases represent a significant burden to morbidity in the population (2) and increase the risk of chronic non-communicable diseases by two to five times (2), mostly cardiovascular diseases, diabetes and cancer in younger people. Mental diseases, especially depression, can be a risk factor for their development in descendants even beyond two generations (3). An increased risk of the development of Alzheimer's disease, the most common of all neurological diseases, continues for at least three generations (4). FH is also very important in terms of identifying rare diseases, as these are very numerous and mostly of monogenetic aetiology (5). It is estimated that 5.3% of new-borns will suffer from a genetic disorder when followed up until the age of 25 years (6).

FH data can be used in population-screening as a primary prevention tool to identify people at increased risk. The US CDC (United States of America Centre for Disease Control and Prevention) developed a structured approach to determining the risk of specific diseases based on a three-generational FH (7). It has been known for a while that, in order to assess the genetic burden, the patient's family ties, the number of relatives with the disease, their age at disease onset and, sometimes, transmission via the paternal or maternal line, are important. These are the criteria for the risk assessment, using a categorization of high, medium or low when considering the risk level for a specific disease. When there is a way to detect the disease in its asymptomatic stage, an early diagnosis can affect the course of the disease. Determining an increased risk enables healthcare workers to carry out specific measures during early diagnosis in an at-risk population: more precise screening methods, and screening performed at a younger age and at shorter intervals than usual (8, 9).
Academic literature commonly reports that an FH of early-onset coronary diseases in close relatives increases the risk of mortality, independent of other known risk factors (10).

Using FH in a primary prevention approach is recommended by the European Guidelines on Cardiovascular Disease Prevention (11). The CDC has defined five conditions, including coronary disease, for which family risk should be determined. In a randomized controlled study within the Family HealthWare project, the CDC developed a tool and intervention software for this purpose (12); the tool was a questionnaire for collecting information on the FH of coronary heart disease, diabetes, colon cancer, breast cancer and ovarian cancer, providing an individualized plan to prevent morbidity (12).

The algorithms for assessing coronary disease risk include standard risk factors, while an FH of early-onset coronary disease is known to increase the patient's risk. FH has been shown to be associated with an early onset of CVD if it spreads beyond the inner circle of relatives (10). When the researchers took into account the number of relatives with coronary disease, the family ties or relationship, and the age of relatives at onset, together with an assessment of family risk and the development of the early onset of coronary disease, hypercholesterolemia, hypertension and obesity, the FH showed an increased risk of 2.5 times for early-onset coronary disease, and a significant association with the other diseases in people with a high or medium family risk (10).

The studies investigated the contribution of FH to an increase in the previously established proportion of high-risk patients. According to Qureshi, a systematic consideration of positive family burden with CVD showed that there were 4.8% more patients at high risk of CVD (13). An FH of diabetes is associated with an increased risk of developing the condition (14, 15). This risk can be assessed in the general population, and using FH in cancer patients can identify families at increased risk of malignant diseases (16). Electronic FHx tools vary in the way in which they are organized, displayed, collected, and integrated into the clinical workflow, so it is highly likely new FHx tools will become available and that current tools will continually improve (16-19).

There are no public health tools or electronic applications available to doctors or the lay public in Slovenia to determine the risk level for specific diseases with genetic aetiology (20-22). However, there is a tool for cancer developed by the Institute of Oncology Ljubljana, which has already been studied among Slovenian GPs as well (20).

There are currently 18 family history tools reported in the literature: six generic, two on cardiovascular disease and ten on cancer (19). The six generic tools were partly tested in primary care and partly validated against a reference standard (genetic counsellor) (19). Of the five specific tools studied in primary care, none were validated (19).

In Slovenia and Europe, data concerning the prevalence of healthy people at increased risk for monogenetic and complex genetic diseases is insufficient (14, 21,22). Some algorithms have been developed, including some partly at the primary care level, but none of them have been validated (19). Family physicians in Slovenia, however, have expressed the view that it is their duty to include genetic elements in their treatment of patients (21, 22). In addition, they and their European colleagues have recognized their unique importance, as physicians of first contact, in identifying genetic risk (23).

2 METHODS

2.1 Aim and Objectives

As part of the study, we will develop a new algorithm-based tool, available as a web application to family medicine teams and appropriate clinical pathways. The burden of genetic diseases in the Slovenian population will be assessed, as well as people's quality of life.

The objectives of the project are as follows:

1. The development of an algorithm to determine the genetic risk of diseases having a significant genetic component at the primary healthcare level, based on FH.
2. An assessment of the risk present in the Slovenian population of diseases having a significant genetic component (monogenic diseases and diseases with complex aetiology).
3. The determination of Health-Related Quality of Life (HRQOL) of people/families with a significant genetic predisposition.
4. The development of clinical pathways for patients of different levels of risk of developing monogenic and complex genetic diseases.

2.2 Procedures

2.2.1 Development of an Algorithm to Determine the Genetic Risk of Diseases Having a Significant Genetic Component at the Primary Healthcare Level, Based on FH

An algorithm will be developed for determining the genetic risk of cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology. The tool will be able to calculate average, medium or high risk for these diseases, based solely on a three-generational FH. A modified Scheuner method (7) will be used. The Scheuner method calculates the level of risk of developing diseases based on FH using data on the generation of the relatives affected by the disease, the onset of the disease in relatives, and the number of relatives affected.

The algorithm will be tested on a sample of family medicine practice attendees who will enter the data on their three-generation family history to the algorithm, allowing for validation by clinical geneticists.

2.2.2 Assessment of the Risk Present in the Slovenian Population of Diseases Having a Significant Genetic Component

In a cross-sectional study, a representative sample of family practice patients will be used to assess the burden of genetic diseases in the Slovenian population, including cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology. The assessment of the burden of genetic diseases will include subjects at genetic risk of these diseases, which will be evaluated by a three-generational FH for these diseases and the presence of congenital and acquired risk factors.

2.2.3 Determination of HRQOL of People/Families with a Significant Genetic Predisposition

The HRQOL of subjects at risk of cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology will be determined. The HRQOL is one of the dimensions of the Quality of Life (QoL) concept, focusing on health. For the selected subjects we will record the influence of health, diseases and their symptoms on their physical, emotional and social well-being. This will allow for the characterization of a continuum of highly complex health outcomes defined by biological/physiological factors, symptoms, the ability to function in everyday life and a general perception of health and well-being.

2.2.4 Establishment of Clinical Pathways for Patients of Different Levels of Risk of Developing Monogenic and Complex Genetic Diseases

The risk assessment algorithm based on family history will classify the subjects into three groups: low-risk, medium-risk, and high-risk. For each group, a clinical pathway of action at the primary healthcare level will be developed. If a high risk for genetic disease is identified, genetic counselling will follow. In cases of medium or low risk, the patient will be managed by the family medicine team, also taking into account acquired risk factors. Clinical pathways will include a horizontal and vertical relationship between healthcare levels and will be aligned with all healthcare level providers.

2.3 Participants

2.3.1 Participating Teams from Family Medicine Practices

The study will involve teams from FMP (family model practices), i.e. a family physician (FP), a practice nurse and a registered nurse. The participation of at least 40 FMPs is planned; selected through a purposive sampling. The teams will participate on a voluntary basis.

Before the study, the participating FMP teams will attend a short workshop to familiarize them with the methodology and implementation of the dataset.

2.3.2 Participating Patients

The participants will be comprised of people who come to FMPs for a preventive check-up. Their participation in the study will be voluntary, and informed consent will be provided, i.e. the patients will sign a statement. Each FMP is expected to include 30 consecutive people. Inclusion criteria will be the age between 30 and 65 years, and informed consent for participation in the study. Exclusion criteria will be an age less than 30 or above 65 years, and an inability to participate in the study (blindness, psycho-organic impairment, intellectual disability). It is planned to gather data from at least 1,000 people.

3.3 Instruments and Procedures

3.3.1 Instruments

During the preventive examination, the following data will be collected: medical history of the acquired and congenital risk factors for the diseases concerned, nutritional history, history of physical activity, smoking, drinking alcohol, perception of stress, signs of depression, social health determinants, body mass index, blood pressure values, laboratory test values (blood sugar, lipidogram) and cardiovascular risk, based on Framingham risk scores (24).

For assessing the HRQOL, we will use the EQ-5D scale. This consists of four parts (25). The first part is intended to familiarize the respondents with the descriptions of health states. Each health state has five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). In the first part of the questionnaire, the respondents evaluate their health state in all five dimensions on the day of the interview (25). They also mark whether they feel better, worse or equal to how they felt in the last 12 months on average (25). They will also be familiarized with the visual analogue scale (VAS), where they mark how good or bad their own health state is on a scale from 0 to 100 (where 0 represents the worst health state imaginable and 100 represents the best) (25). For assessing risky alcohol drinking, we will use the Slovenian version of AUDIT-C (26). This is a three-item alcohol screen that helps to identify people who are risky drinkers. In men, a score of six or more is considered positive, while in women the cut-off score is five.

For depression, we will use three questions for screening (27).

3.3.2 Procedures

The participating FMP teams will complete a questionnaire covering the basic demographic data of the FMP team and some information related to work in the practice: the working years of the team members, the years of FMP status (the first FMPs in Slovenia were introduced in 2011, with practices gradually joining) (8), the number of registered patients, the number of preventive examinations performed per year, and quality indices associated with prevention implementation.

Each patient will complete a questionnaire covering their basic demographic data, a three-generational FH for the monogenetic and complex genetic diseases (cardiovascular diseases, hypertension, diabetes, cancer, neurological, mental and sensory diseases, and other diseases present in the family with a possible genetic aetiology), and an EQ-5D scale (25). The determined level of genetic risk that we find as the result of the algorithm for each individual patient will be assessed (validated) by clinical geneticists; they will check the family history data and determine whether the algorithm calculated an objective genetic risk.

4 DISCUSSION

4.1 Discussion on Expected Results

The project results are expected to contribute to the development of methodologies allowing a practical risk assessment of (currently) healthy people to evaluate their genetic predisposition, primarily for monogenetic diseases, but also for diseases with complex aetiology.

In Slovenia, FPs rarely include genetic aspects when treating patients, and they do only have limited protocols to help them manage such patients and refer them to genetic assessment (20,21). The planned project will contribute to easier and, most of all, reliable identification of people and families at a high risk of monogenetic diseases.

The target diseases constitute a global public health challenge. Early identification of people at increased risk, before they develop any signs and symptoms of the disease, may contribute significantly to effective prevention of the disease and its consequences.

By use of the algorithm to determine genetic risk, the primary prevention of chronic disease and early detection of monogenetic diseases will be strengthened, resulting in longer and higher-quality lives of family practice patients.

It has already been shown that healthy people with a less optimal lifestyle should also be encouraged to improve their lifestyle as this would improve their health-related quality of life (28).

The target diseases are all extremely important health problems. They involve rare diseases (their diagnosis is supported by the European Union and the Slovenian national plan) and multifactorial diseases, which are the biggest cause of morbidity/mortality. The aim of a very early detection of people with a significant genetic predisposition is currently a highly relevant public health application of personalized medicine.

Within this project, we will also develop clinical pathways for the management of patients with low, medium or high genetic risk. Such pathways cannot be developed without also taking into account the acquired risk factors. This will be an additional value of our project.

4.2 Discussion on Methodology

This study will use a cross-sectional design, which is appropriate according to the purposes and aims. We will not determine any causal relationship, as this is not one of the aims of our study. The sampling of the FMPs will be purposive, and this could contribute to a selection bias. However, the fact that the FMPs will be scattered across the whole of Slovenia will lower the bias as much as possible. The sampling of the participants in each practice will be consecutive, which is appropriate according to the study aims. The study will use subjective as well as objective data; the most problematic is data from the family history, as participants are not always aware of all the information about their relatives' illnesses (29, 30). This possibility of inaccurate or incomplete data collection will be minimized by offering the participants the opportunity to think about the topic at home prior to coming to the practice.

The developed algorithm will be based on the modified Scheuner method (7) and the results obtained from the algorithm will be validated by clinical geneticists, enhancing the validity even more.

5 CONCLUSIONS

This project will facilitate the identification of individuals and families at increased genetic risk at a primary health level. This will contribute to a better understanding of the epidemiology and of the extent of the health problem. New possibilities in the field of primary and secondary prevention for lowering the public health burden of these diseases will evolve.

The project will contribute to the transfer and efficient use of the contemporary findings of genetic medicine in clinical practice, which will reduce the gap between basic science and applied clinical medicine. If the identification of genetic predisposition proves to be effective in preventing complex genetic diseases, it may constitute a foundation for the development of biomarkers with a great market potential in medicine.

The project's results will serve as the basis for preparing new professional guidelines for the early detection of complex-multifactorial genetic diseases in FM, the education of healthcare workers at undergraduate and postgraduate levels, and the active inclusion in top international studies on the diseases that constitute the leading global healthcare problems.

CONFLICT OF INTEREST

The authors declare that no conflict of interest exists.

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ETHICAL APPROVAL

The study was approved by the National Ethics Committee of the Republic of Slovenia (No. 0120-544/2016/3).

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