Community genetics and community medicine*

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In the decades to come, molecular genetic insights and techniques will have great influence on prevention and health care. Health care providers should anticipate important new developments rather than just wait and see. For community doctors, who can impossibly oversee all relevant developments in sufficient detail, close communication with the community and clinical genetic specialists is necessary to keep pace with progress. With regard to genetic counselling and reproductive medicine, working agreements between primary care and specialist centres are important. General communication about hereditary issues can be dealt with by well informed GPs, with appropriate computerized decision support, but in order to address specific risks and disorders consultation at a clinical genetic centre is preferred. In clinical medicine, much work is being done on DNA-based ‘dia-prognosis’ and more targeted interventions. Estimations of when such innovations will really have an impact range from 2005 to beyond 2020, and there are still many uncertainties, especially regarding common multifactorial disorders. Community-based genetic epidemiology has become a basic science in understanding the human genome. Clinical epidemiological methodology can contribute a lot to the quality of molecular clinico-genetic studies. Long-term follow-up to evaluate predictions and interventions needs more attention, and can easily be integrated into primary care medicine. In view of the ambition to develop more tailor-made interventions, research methodology will be challenged regarding \( n = 1 \) studies. With respect to counselling and clinical practice, many ethical issues, relevant for community medicine, have to be considered in the domains of both reproductive medicine and clinical practice. Doctors, patients and society, traditionally battling to reduce diagnostic and prognostic uncertainties, must now learn to cope with approaching certainties. As for all new technologies, cost-effectiveness is an important topic for genetics. Increased cost-effectiveness because of better targeted interventions may be counterbalanced by the price of the new technologies and an expanding indicated population. In view of current developments, community practitioners must integrate community genetics into their daily routine, and critically anticipate possibly relevant innovations. More efforts in genetic risk assessment and communication are necessary in undergraduate and postgraduate training. A multidisciplinary approach is needed, in collaboration with primary care-oriented genetic specialists. Efforts to educate the public and (potential) patients should start at an early age, and must focus on what (future) health care users need for a balanced appraisal of genetic information and for optimal decision making in health promotion and health care.

Keywords. Community genetics, community medicine, diagnosis, dia-prognosis, ethics.

Introduction

The rapidly increasing knowledge of the human genome has evoked a lot of promises as to the understanding of disease\(^1\) and improvement in health, prevention and health care.\(^2\) Although in some fields these promises are closer to reality than in others, there is still much uncertainty about which developments will have what impact at which moment, and which developments will be more or less successful. However, it is without doubt that in the decades to come, molecular genetic insights and techniques will have great influence in the broad field of public health and health care, while in various fields this influence is already visible. In order to make optimal use of innovations, and to avoid unrealistic expectations, health care providers should anticipate important new biomedical developments, rather than wait and see what will happen. Apart from knowing about
relevant biomedical innovations as such, integrating these into health care and into education of professionals needs a careful approach. In addition, the ethical implications and the consequences for decision making by patients and the public should be addressed.

Community genetics represents the interface between basic and clinical genetics on the one hand, and community medicine at the other. For community medicine and primary health care, traditionally strongly focused on the family context and the social and physical environment of patients and their health problems, increasing insight into genetic patterns and gene–environment interactions is very challenging. In this contribution, an overview is given of relevant developments, with implications for community health care.

Biomedical progress

The impact of increasing genetic insights and medical technology is to be anticipated over a broad field of innovations, although in some areas the translation of new knowledge into practical health care applications will take more time than in others. Therefore, for community doctors, who will be confronted with relevant innovations over the whole range of health care and for whom it is impossible to oversee all developments in sufficient detail, close communication and collaboration with clinical genetic centres and clinical specialists will be necessary to keep pace with progress.

Genetic counselling and reproductive medicine

A basic task of the primary care physician and primary care obstetrician is to support and advise those who want to have a child in making decisions, when they fear, suspect or know about a genetic predisposition among relatives of the intended mother, father or both.

In the past, the basic tool was to combine general knowledge about patterns of inheritance of certain disorders with the specific knowledge of the observed occurrence in a family, in order to obtain an assessment of risk. Although for many disorders this is still the most important approach, as a result of identifying specific genetic defects for particular disorders, it is increasingly possible to perform DNA tests to exclude or confirm carriership in individual cases even in the absence of clear clinical manifestations.

Primary care doctors, apart from giving general information and being able to refer accurately to a clinical genetic centre, can get access to advanced diagnostic knowledge (supported by up-to-date databases, such as www.geneclinics.com) and sometimes test techniques. In this context, it is important to consider what the GP can do himself, with or without consultative support from the clinical genetics centre or a clinical specialist in the region, and when immediate referral would be more appropriate. It is useful to prepare explicit working agreements between primary care and specialist centres regarding these issues. Although agreements may vary by region, in my view the baseline would be that communication and information about general questions and concerns about hereditary issues can be dealt with by well informed GPs, but when specific suspicions or questions on possible specific genetic risks are raised, consultation of a clinical genetic centre is preferred.

Innovations in the context of reproduction medicine based on genetic knowledge, with major medical and ethical implications, are partly already available for health care (such as pre-conceptional carrier couple screening for cystic fibrosis, advanced prenatal screening with risk assessment tests selectively followed by confirmatory invasive tests) and partly still in the phase of research and development [e.g. pre-implantation genetic diagnostics, in vitro ovum-nucleus transplantation (IVONT) in mitochondrial DNA-related disorders]. These are popular topics in the media and can lead to many questions in practice. Therefore, it is important that community health care workers in primary medical care and obstetrics are sufficiently informed about these developments, in order to inform those who consult them, and to know about possibilities, limitations, consequences and criteria for referral.

Dia-prognosis and more targeted intervention

Innovation of biomedical knowledge and understanding pathophysiological processes is decisive for the development of tests with more powerful predictive impact. DNA diagnostics is in fact prognostics since it touches the basic functional level of our biomedical nature.

Based on established specific genotypes, it is generally expected that more predictive ‘dia-prognosis’ and more targeted, tailormade intervention strategies will be increasingly possible. For community medicine, this would be a very important development, since it can enable more selective assignment of intensive and often burdensome preventive or treatment interventions (e.g. lifestyle changes, diet, long-term medication, etc.) and focus on those subjects who will be likely to respond and derive benefit. An example where such possibilities are, in fact, already within our scope is familial hypercholesterolaemia (FH), where cholesterol synthesis inhibitors are of vital importance. While the scientific base and the design of such more tailormade intervention strategies are still in development, much research in this field is being carried out. Pharmacogenetics aims to improve the targeting and dosing of medication. Work in this field is currently being done, for example, in cardiovascular medicine, oncology and psychiatry, in both academia and industry. Regarding tailormade interventions, there is even the ambition to develop medication especially targeted to the individual and his DNA profile.

Estimations of when these promises will have impact in routine patient care vary from 2005 to beyond 2020, where predictive testing in cases of a strong family
history of a particular condition is estimated to be a relatively early development and individualized ‘designer drugs’ a late one.\textsuperscript{2,10} Apart from scientific developments, economic influences play a major role. On the one hand, enormous investments are being made, while on the other hand concerns are heard that drug production might become commercially less attractive since patient populations could be fragmented into increasingly small subgroups.\textsuperscript{11} Scientific scepticism is also still heard among authors saying that the complexity of the genetics of most common (multifactoral) diseases (incomplete penetrance, weak correlations between genotype and phenotype, and low percentages of occurring cases explained by genotype) casts doubts on whether accurate prediction will ever be possible.\textsuperscript{12}

Even further in the future and more uncertain are possible innovations in the domain of (somatic and germline) gene therapy. In what direction things will go, and whether, when and for which clinical problems the balance of possible effects, benefits, risks and ethical implications will be positive, is as yet largely unclear.

In this era of intriguing developments expected within one decade on the one hand, and strong scepticism on the other, primary care physicians who do not like to be surprised and who want to keep pace with questions from patients are advised to keep themselves informed on a general level and to critically follow what is going on.

\textit{(Clinical) epidemiological dimension}

Considerable efforts are still needed not only in the laboratory and the clinic, but also in (clinical) epidemiological research. While in the early days of population genetics, epidemiology has already been an essential instrument, molecular genetic epidemiology is now a basic science in the analysis and understanding of the human genome. Also, epidemiological methodology can contribute a lot to the quality of molecular clinico-genetic studies. Recently it was shown that the clinical epidemiological quality of many molecular genetic studies was poor. Of 40 evaluated research papers, 35 failed to comply with one or more of seven essential methodologic criteria.\textsuperscript{13} Furthermore, long-term follow-up to validate diagnostic and prognostic predictions clinically\textsuperscript{10} and to monitor outcome of interventions needs more attention. At the same time, it has to be acknowledged that, in view of the ambition to develop more tailored, perhaps even individualized diagnostic and (pharmaco)therapeutic processes, study of population-oriented validations will become increasingly under pressure. Research methodology will therefore be severely challenged to extend its routine tools for $n = 1$ studies.

Ethical questions and challenges

In the context of both counselling and clinical practice, important ethical issues have to be considered, and this also applies to community medicine. Two broad fields of ethical concern can be distinguished:

- counselling and patient/doctor decision making in the context of reproductive medicine; and
- counselling and patient/doctor decision making in preventive and clinical management.

In the field of reproductive medicine, much attention is being paid to ethical key issues are the right of (self-) determination and responsibilities of intended parents, the well-being of the putative child, the ethico-legal position of the embryo, the requirements regarding the provision of adequate and balanced information, freedom of choice and consent of intended parents, and the responsibilities and duties of the doctor and other health care professionals. In order to facilitate optimally informed decision making, maximum clarity should also be provided to patients as to the probabilities and diagnostic uncertainties, for example in terms of errors of false-positive and false-negative results; and uncertainties in prognosis and possible treatment effects, with possible clinical, ethical and psychosocial implications.\textsuperscript{8,10} In addition, insight into risks and adverse effects associated with intervention and non-intervention is important. Furthermore, it has to be considered that if an index patient is found to have a genetic condition, tests on (healthy) relatives may be appropriate. This requires a careful approach in which index patients, clinical geneticists (as counsellors) and GPs (responsible for referrals) work together to contact and inform relatives, weighing up both patient’s and relatives’ interests.\textsuperscript{6}

While clinical occurrence of disease is generally a result of both intrinsic and extrinsic (e.g. lifestyle, social and environmental) factors, for preventive and clinical management much attention is being paid to the expected high degree of predictability of DNA diagnostics and prognostics for investigated subjects and possible siblings. This is currently mainly relevant for a modest number of (monogenetic) disorders, but in future possibly also for more complex multifactorial diseases.

A very high degree of predictability can be a huge problem for subjects since they may feel that it is completely certain that they will get a severe disease at a certain (too young) age without being able to escape, with major psychosocial consequences of such predestination. Others might prefer, however, to know as much as possible about their perspectives, in order to plan things better for themselves and their relatives. Therefore, both the right to know and the right not to know must be respected, which requires full attention to practical solutions to achieve this objective maximally.

Such predictability does not always indicate a static, unchangeable fate. It may also be a timely signal for possible improvement, for example to adapt one’s lifestyle or to take preventive medication (e.g. in FH). However, also in the context of intervention-oriented genetic diagnostics, as in pharmacogenetics, subgroups
can be identified with less favourable intervention perspectives.

Predictability is attractive for various societal purposes with primary objectives other than promoting individuals’ health, e.g. for life insurance companies who want to seek the strongest possible basis for deciding to accept subscribers and for premium setting. Accordingly, ethical issues regarding privacy of genetic information have to be addressed.

In summary, although medicine has the aim and the tradition to diagnose in order to enhance certainty on health status and prognosis, and although this is where a substantial part of medical research has been focused for centuries, we seem to shrink from too much certainty and its possible implications. Doctors and patients, traditionally battling to reduce diagnostic and prognostic uncertainty, must now learn to cope with approaching certainty.

Cost-effectiveness

As is nowadays usually considered when introducing new technologies, cost-effectiveness is also an important topic for innovations in genetics. Where one would generally expect increased cost-effectiveness when more accurate dia-prognostics and better targeted interventions were possible, the high price of the new technologies and expanding the indicated population by lowering the threshold of interventions might produce new costs.

In evaluating cost-effectiveness of genetic testing it is, for example, important to know about lifetime risk for the target disorder, the prevalence of susceptibility-conferring genotypes and the relative risk associated with the genotype factor. Cost-effectiveness methodology can contribute to the evaluation of alternative strategies in the context of community genetics. For clinical purposes, transparency of results can be enhanced by using ‘numbers needed to screen’ (NNS), expressing the number of subjects to be screened in order to prevent one case. For population screening on BCRA1, a relatively penetrant gene for breast cancer, NNS among women would be 2500, while it would be five in high risk families. However, comparing NNS results between different clinical problems is not straightforward: for instance, for phenylketonuria (PKU) screening, the NNS is ~12 000, but the positive and negative predictive value of dia-prognosis and the efficacy and acceptability of treatment for PKU are much higher.

Challenges for community medicine

Doing an optimal job in genetic counselling, which also includes timely referral, fits very well with the traditional mission of primary health care workers. In addition, new possibilities resulting from increasing knowledge of the human genome should be integrated without too long a delay. Anticipating DNA diagnostics and prognostics in the context of medical decision making is largely a new challenge. Apart from applying new knowledge and new tools, qualitative differences also appear to enter the primary health care process: in contrast to traditional clinical diagnostics, genetic assessment (on request, by suspicion or when screening for some health care purpose or other) and associated decision making will often be done without a presenting complaint and independently of current actual health status. The latter is also in contrast to ‘actual phenotype’ screening such as blood cholesterol, blood sugar and blood pressure screening. Besides, the experienced dia-prognostic impact of genetic diagnosis makes a difference, since the genotype generally cannot be changed while the phenotype often can. However, new opportunities for targeted preventive and therapeutic interventions may be provided.

Various community health care disciplines have a role. Public health services and community and practice nurses may provide basic information at contacts during routine preventive child care, actively and on request. The community obstetrician/midwife and the GP can provide more specific information and counselling on available diagnostic and referral possibilities. In countries where the GP is responsible for continuity of care and holds up-to-date longitudinal computerized patient records for the registered population, he has unique possibilities to identify subjects at increased risk for a genetic disease. On the basis of the family history, to be represented in a pedigree, primary care doctors can stratify risk (e.g. for breast cancer), to identify those who can be reassured and to refer those with an elevated risk for further testing to a genetic centre clinic. As to the possibility for GPs and public health services to contribute actively to counselling on and to implement preconceptional carrier couple screening, recent research showed positive experiences. Furthermore, primary care practitioners can play a key role in monitoring and caring for patients with a genetic disorder, and coordinate care in collaboration with specialists in genetics (who can act partly as consultants periodically visiting primary care centres), clinical specialists, and paramedical and psychosocial workers.

Community medicine can also participate in research, e.g. by supporting (the organization of) population-based genetic epidemiological studies and studies on the effects of counselling strategies. Besides contributing to new biomedical knowledge, community-based research support can be also very important in evaluating aspects of new screening programmes being considered for hereditary disorders, such as primary haemochromatosis.

In view of the developments, promises and uncertainties described in the previous sections, I support the analysis of Emery and Hayflick, who summarize the
current challenges for integrating genetic medicine into primary care as follows:18

- primary care practitioners need to become ‘genetically literate’;
- the most important elements for primary care currently are prediction of risk of certain cancers (breast, ovary, colon) and carrier screening for common autosomal recessive disorders;20,21
- pharmacogenetics is an important field of development and will become increasingly relevant in prescribing decisions;
- development of generic skills in genetic risk assessment and communication is required;
- a multifaceted approach is needed, including community genetic counsellors, primary care genetic specialists, educational programmes and computerized decision support.22,23

Education of professionals and the public

With increasing genetic information about common illnesses, primary care physicians will become practitioners of genomic medicine, with important medical and communicative tasks towards patients.2 To be prepared for this mission, basic knowledge on important genetic disorders and patterns of inheritance, genetic testing, and foreseeable therapeutic innovations should be integrated into undergraduate and postgraduate (vocational) training, and in continuing medical education.24–26 In addition, skills in risk assessment and risk communication, and in how to utilize computer support, have to be covered.23 The corresponding educational needs of other health care disciplines also have to be met.16

Finally, efforts to educate the public and (potential) patients are important. In addition to addressing the need of the public to learn about the possibilities and limitations of current genetic medicine, the needs of future generations should be emphasized. Since developments are moving fast, those who are born today or tomorrow will face types of ‘routine’ health (care) decisions different from those of older generations. Sources of public information will keep pace with progress in technology, and use of the Internet for information on health and disease will become more routine. Also, genetic self-testing will become increasingly available, so that in addition to formal quality control regulations, requirements of appropriate use and interpretation must be considered. Generally speaking, the question should be answered: what knowledge and skills do (future) health care users need for a balanced appraisal of genetic information and for optimal decision making in the context of health promotion and health care? Also, what must they therefore learn about genetic realities of today and expectations for the future? It must also be acknowledged that subjects differ substantially in risk perception, information needs, priorities and values.12,27

This implies that in addition to common educational efforts by schools, media and health institutions, tailor-made information exchange and appropriate communication with health care professionals is indispensable.28

References

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