

Genomics: New Technology for Obstetrics and Gynaecology

This technical update has been prepared by the Genetics Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR

R. Douglas Wilson, MD, FRCSC, Philadelphia PA

GENETICS COMMITTEE

R. Douglas Wilson (Chair), MD, FRCSC, Philadelphia PA

Alain Gagnon, MD, FRCSC, Vancouver BC

Gregory Davies, MD, FRCSC, Kingston ON

Valerie Desilets, MD, FRCSC, Montreal QC

Gregory J. Reid, MD, FRCSC, Winnipeg MB

Anne Summers, MD, FRCPC, Toronto ON

Philip Wyatt, MD, PhD, Toronto ON

Victoria Allen, MD, FRCSC, Halifax NS

Sylvie Langlois MD, FRCPC, Vancouver BC

3. New technology such as microarray is a powerful approach for genomics research and will completely change the methodological approach to basic research and clinical diagnosis.

4. Genetic knowledge and testing is changing. These changes will require caregivers to gain new knowledge, skills, and attitudes in the area of genetics.

J Obstet Gynaecol Can 2005;27(1):63-68

INTRODUCTION

The completion of a high-quality, comprehensive sequence of the human genome corresponded with the 50th anniversary year of the discovery of the double-helical structure of DNA and must be considered a landmark event.¹ Many scientists would indicate that the genomic era is now a reality. It is important that these new genetic concepts and findings be part of the ongoing education of obstetricians and gynaecologists.

The term genome appears to have been first used by Winkler in 1920 and to have been created by the elision of gene and chromosome to signify a set of chromosomes and the genes they contain.² The more recent use of the term genomics was to designate a field of gene mapping and sequencing. Other definitions would include genetics as the study of inheritance and genomics as the study of genomes. Adjectives have been added to the word genomics that indicate specific aspects or applications of genomics, including structural genomics (mapping and sequencing), functional genomics (information about function to knowledge of DNA sequence), and pharmacogenomics (drug response to genetic differences). A description of coordinated gene expression in various tissues, at various stages of development, and in various physiological states became possible with the development of microarray methods (chip technology) and other methods such as SAGE (serial analysis of gene expression).

Abstract

Objective: To introduce new information and technology involving genomics (human genome project, genetic testing, microarray technology).

Options: Limited to introductory discussion of new genetic information and technology.

Evidence: MEDLINE was searched to identify publications related to this topic after 2000. This document represents an abstraction of the information.

Values: This update is a consensus of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Benefits, Harms, and Costs: This update educates readers about new genetic concepts, directions, and technology. At present, there is no harm or cost (research with limited clinical application) identified.

Conclusions:

1. The complete and comprehensive sequencing of the human genome leads to new genetic concepts and opportunities.
2. Genomics involves gene mapping and sequencing and can be applied to biology, health, and societal needs.

Key Words: Genetic screening, genetic diagnosis, molecular probe techniques, prenatal diagnosis

This technical update reflects emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.

This update will briefly summarize 3 areas of genomics: the human genome project, genetic testing, and microarray technology.

DISCUSSION

1. The Human Genome Project and Genomic Research¹

In 1988 the US National Research Council produced a report entitled “Mapping and Sequencing of the Human Genome.”³ The successful completion of the human genome project in 2003 allowed for the development of a blueprint for future genomic research over the next several years. The ability to explore genome function is increasing in specificity as each subsequent genome is sequenced for different organisms. Although genome-based analysis methods are rapidly permeating biomedical research, the challenge of establishing robust paths from genomic information to improvements in human health remains immense. *Nature* recently published an article entitled “A Vision for the Future of Genomic Research,”¹ which stated that following the sequencing of the human genome, the next 3 steps have been identified and will require applying this information to biology, health, and society.¹

Applying genomics to biology¹ (elucidating the structure and function of genomes) requires 5 areas of direction:

1. to comprehensively identify the structure and functional components encoded in the human genome;
2. to elucidate the organization of genetic networks and protein pathways and establish how they contribute to cellular and organismal phenotypes;
3. to develop a detailed understanding of the heritable variation in the human genome;
4. to understand evolutionary variation across species and the mechanisms underlying it; and
5. to develop policy options that facilitate the widespread use of genome information in both research and clinical settings.

Applying genomics to health¹ (translating genome-based knowledge into health benefits), requires 6 areas of direction:

1. to develop robust strategies for identifying the genetic contributions to disease and drug response;
2. to develop strategies to identify gene variants that contribute to good health and resistance to disease;
3. to develop genome-based approaches to prediction of disease susceptibility and drug response, early detection of illness, and molecular taxonomy of disease states;

4. to use the new understanding of genes and pathways to develop powerful new therapeutic approaches to disease;
5. to investigate how genetic risk information is conveyed in clinical settings, how that information influences health strategies and behaviours, and how these affect health outcomes and costs; and
6. to develop genome-based tools that improve the health of all.

Applying genomics to society¹ (promoting the use of genomics to maximize benefits and minimize harms) requires 4 directions of evaluation:

1. to develop policy options for the uses of genomics in medical and non-medical settings;
2. to understand the relations between genomics, race, and ethnicity and the consequences of uncovering these relations;
3. to understand the consequences of uncovering the genomic contributions to human traits and behaviours; and
4. to assess how to define the ethical boundaries for uses of genomics.

Finally, Collins *et al.* indicate that the opportunities described within the article are thought to be highly achievable but that the final initiation of specific programs will require a much more detailed analysis.¹ Relative priorities of each component must be addressed in the light of limited resources to support research. The authors emphasized that this vision should be revisited regularly to ensure that the true promise of genomics that will benefit humankind can be realized.

2. Genetic Testing

Genomics in clinical practice indicate that approximately 600 genetic tests are currently available for clinical testing, and most are used for diagnosis of rare single gene disorders or chromosomal abnormalities, with a few being used for newborn screening.⁴ However, a growing number of genetic tests may have population-based applications that include determining the risk of developing a disease or condition in the future (e.g., predictive testing for breast cancer or cardiovascular disease) and recognizing genetic variations that can influence response to medicines (pharmacogenetics). A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites to detect heritable disease related to genotypes, mutations, phenotypes, or karyotypes for clinical purposes.⁵ This definition reflects the broad range of techniques that can be used in the testing process. Genetic testing is often the best way to confirm a diagnosis in a patient with signs or

symptoms suggesting a genetic disease. The sensitivity of tests for rare conditions will continue to improve as additional causative mutations are identified. Genetic tests are available to determine the risks of common diseases, but these often have limited predictive value. Evaluating the clinical usefulness of these tests will require careful assessment of the risks and benefits of testing. The availability of specific measures to reduce risk in genetically susceptible people will be a major consideration.

3. Microarray Technology

Microarray technology is a powerful approach for genomics research.⁶ Microarrays, or microchips, represent a new area of high technology that will completely change the methodological approach to basic research and clinical diagnosis. This technology can be used for genotyping, expression profiling, and proteome analysis.⁷ Monitoring of gene expression using DNA microarrays allows the simultaneous assessment of the transcription of tens of thousands of genes and of their relative expression between normal cells and pathological cells. This technology allows laboratories to change from studying the expression of 1 or 2 genes in a month to studying the expression of tens of thousands of genes in a single afternoon. The DNA microarray is able to monitor the expression of the genes by measurement of a given sample to hybridize to target sequences on a chip.⁸ In essence, RNA extracted from a biological sample of interest is reverse-transcribed into cDNA and ideally represents a quantitative copy of the genes expressed at the time of sample collection. This cDNA is labelled with a tracking molecule, such as a radioactive or fluorescent nucleotide or an affinity molecule like biotin. The labelled cDNA has been hybridized to a DNA chip that contains thousands of gene targets. Ideally, each molecule in the labelled cDNA will only bind to its appropriate complementary target sequence on the array. Quantitative imaging coupled with clone database information allows measurement of the amount of labelled cDNA that hybridizes to each target sequence, resulting in the identification and relative quantification of the genes expressed in the original biological sample.⁹⁻¹¹ This type of technology allows investigators to quickly measure the expression of a complete genome across a large number of environmental stimuli.¹²⁻¹⁵ A review of publications listed on PubMed revealed that, from 1995 until 2002, more than 2000 papers documented this type of technology.⁸ Although the DNA microarray chip⁸ is currently a tool most commonly used to monitor the level of a gene's expression at the RNA level,^{9,16,17} it can also be used to document DNA copy number,¹⁸⁻²⁰ DNA protein interactions,^{21,22} and sequencing applications (polymorphism detection). The usefulness of this technology in determining DNA copy numbers (segmental aneuploidy) was shown

in a study of fetuses from women who had experienced a spontaneous pregnancy loss (< 20 weeks). A chromosomal abnormality not detectable by standard cytogenetic techniques was found in 9.8% of cases.²³ This technology has also been applied with positive results to identify microdeletions and microduplications in patients with mental retardation.^{24,25}

The future for microarrays is bright, and it is important that health care workers in the field of obstetrics and gynaecology are aware of these technologies that may impact the knowledge and practice of obstetrics and gynaecology. Microarray analysis should not be considered as the conclusion but as a discovery mechanism to help determine areas of interest in maternal and fetal disease.⁸ As this technology changes, the format of microarrays will become more complete, more miniaturized, more technically standardized, and more useful for the prediction and diagnosis of genetic disease and risks.

4. Knowledge, Skills, and Attitudes in Genetics

One of the difficult challenges for health care professionals confronted with these new technologies and changes in genetic testing is the constantly evolving knowledge base. A recent publication from the National Coalition for Health Professional Education in Genetics looked at the knowledge, skills, and attitudes that all health professionals in the area of genetics should have.²⁶ The Genetics Committee has reviewed these recommendations and feel they are realistic for the present and can be applied to the future.

Knowledge

All health professionals should understand the following:

1. basic human genetics terminology
2. the basic patterns of biological inheritance and variation, both within families and within populations
3. how identification of disease-associated genetic variations facilitates development of prevention, diagnosis, and treatment options
4. the importance of family history (minimum 3 generations) in assessing predisposition to disease
5. the role of genetic factors in maintaining health and preventing disease
6. the difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation)
7. the role of behavioural, social, and environmental factors (lifestyle, socioeconomic factors, pollutants, etc.) to modify or influence genetics in the manifestation of disease

8. the influence of ethnoculture and economics in the prevalence and diagnosis of genetic disease
9. the influence of ethnicity, culture, related health beliefs, and economics in the clients' ability to use genetic information and services
10. the potential physical and (or) psychological benefits, limitations, and risks of genetic information for individuals, family members, and communities
11. the range of genetic approaches to treatment of disease (prevention, pharmacogenomics or the prescription of drugs to match individual genetic profiles, gene-based drugs, gene therapy)
12. the resources available to assist clients seeking genetic information or services, including the types of genetics professionals available and their diverse responsibilities
13. the components of the genetic-counselling process and the indications for referral to genetics specialists
14. the indications for genetic testing and (or) gene-based interventions
15. the ethical, legal, and social issues related to genetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance, and employment)
16. the history of misuse of human genetic information (eugenics)
17. one's own professional role in the referral to or provision of genetics services, follow-up, and quality review of genetic services

Skills

All health professionals should be able to

1. gather genetic family history information, including an appropriate multigenerational family history
2. identify clients who would benefit from genetic services
3. explain basic concepts of probability and disease susceptibility and the influence of genetic factors in the maintenance of health and development of disease
4. seek assistance from and refer to appropriate genetics experts and peer support resources
5. obtain credible, current information about genetics for oneself, clients, and colleagues
6. effectively use new information technologies to obtain current information about genetics
7. educate others about client-focused policy issues
8. participate in professional and public education about genetics

The following skills (9 to 17) delineate the components of the genetic-counselling process and are not expected of all health care professionals. However, health professionals should be able to facilitate the genetic counselling process and prepare clients and families for what to expect, communicate relevant information to the genetics team, and follow up with clients after genetics services have been provided. For those health professionals who choose to provide genetic counselling services to their clients, all components of the process, as delineated in skills 9 to 17, should be performed.

9. educate clients about availability of genetic testing and (or) treatment for conditions seen frequently in practice
10. provide appropriate information about the potential risks, benefits, and limitations of genetic testing
11. provide clients with an appropriate informed-consent process to facilitate decision making related to genetic testing
12. provide, and encourage the use of, culturally appropriate, user-friendly materials and (or) media to convey information about genetic concepts
13. educate clients about the range of emotional effects they and (or) their family members may experience as a result of receiving genetic information
14. explain potential physical and psychosocial benefits and limitations of gene-based therapeutics for clients
15. discuss the costs of genetic services, the benefits and potential risks of using health insurance for payment of genetic services, and the potential risks of discrimination
16. safeguard privacy and confidentiality of clients' genetic information to the extent possible
17. inform clients of potential limitations to maintaining privacy and confidentiality of genetic information

Attitudes

All health professionals should

1. recognize philosophical, theological, cultural, and ethical perspectives influencing the use of genetic information and services
2. appreciate the sensitivity of genetic information and the need for privacy and confidentiality
3. recognize the importance of delivering genetic education and counselling fairly, accurately, and without coercion or personal bias
4. appreciate the importance of sensitivity in tailoring information and services to clients' culture, knowledge, and language level

5. seek coordination and collaboration with an interdisciplinary team of health professionals
6. speak out on issues that undermine clients' rights to informed decision making and voluntary action
7. recognize the limitations of their own genetics expertise
8. demonstrate willingness to update genetics knowledge at frequent intervals
9. recognize when personal values and biases, with regard to ethical, social, cultural, religious, and ethnic issues, may affect or interfere with care provided to clients
10. support client-focused policies

CONCLUSIONS

1. The complete and comprehensive sequencing of the human genome leads to new genetic concepts and opportunities.
2. Genomics involves gene mapping and sequencing and can be applied to biology, health, and societal needs.
3. New technology such as microarray is a powerful approach for genomics research and will completely change the methodological approach to basic research and clinical diagnosis.
4. Genetic knowledge and testing is changing. These changes will require caregivers to gain new knowledge, skills, and attitudes in the area of genetics.

GLOSSARY

Chromosome (human): Linear DNA structures containing all the genes of the individual (human total 46, or 23 pairs)

Complementary DNA (cDNA): A DNA sequence that is exactly complementary to mRNA, lacking introns and regulatory regions.

DNA: A double-helical structure composed of 2 coils of nucleotide chains connected by nitrogen bases.

DNA hybridization: A process whereby labelled nucleic acid molecules (oligonucleotide probe) bind to a DNA sequence on a target (Southern blot, metaphase chromosomes, or interphase nuclei) that is complementary to its own.

Gene: A unit of heredity responsible for the inheritance of a specific trait that occupies a fixed chromosomal site and corresponds to a sequence of nucleotides along a DNA molecule.

Genome: The entire complement of genetic material in a chromosome set.

Genotype: Genetic constitution or composition of an individual.

Karyotype: The chromosome constitution of an individual.

Messenger RNA (mRNA): A single-stranded nucleotide that is derived from single-stranded DNA and must be translated into protein to produce to gene product.

Mutation: An alteration of DNA sequencing in a gene that results in a heritable change in protein structure or function that frequently has adverse effects.

Phenotype: Observable physical characteristics of an organism resulting from the expression of the genotype and its interaction with the environment.

REFERENCES

1. Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research. *Nature* 2003;422:835–47.
2. McKusick VA, Ruddle FH. A new discipline, a new name, a new journal. *Genomics* 1987;1:1–2.
3. National Research Council. Mapping and sequencing the human genome. Washington (DC): National Academy Press; 1988.
4. Centers for Disease Control and Prevention. Genomics and disease prevention: genomics in practice. Available at: <http://www.cdc.gov/genomics/phpractice.htm>. [OGDP Web site]. Accessed September 4, 2004.
5. Burke W. Genetic testing. *N Engl J Med* 2002;347:1867–75.
6. Leung YF, Cavalieri D. Fundamentals of cDNA microarray data analysis. *Trends Genet* 2003;19(11):649–59.
7. Carella M, Volinia S, Gasparini P. Nanotechnologies and microchips in genetic diseases. *J Nephrol* 2003;16(4):597–602.
8. Afshari CA. Perspective: microarray technology, seeing more than spots. *Endocrinology* 2002;143(6):1983–9.
9. Shalon D, Smith SJ, Brown PO. A DNA microarray system for analyzing complex DNA samples using two-color fluorescent probe hybridization. *Genome Res* 1996;6(7):639–45.
10. Khan J, Saal LH, Bittner ML, Chen Y, Trent JM, Meltzer PS. Expression profiling in cancer using cDNA microarrays. *Electrophoresis* 1999;20:223–9.
11. Hegde P, Qi R, Abernathy K, Gay C, Dharap S, Gaspard R, et al. A concise guide to cDNA microarray analysis. *Biotechniques* 2000;29(3):548–50;552–6.
12. Spellman PT, Sherlock G, Zhang MQ, Iyer VR, Anders K, Eisen MB, et al. Comprehensive identification of cell cycle-regulated genes of the yeast *Saccharomyces cerevisiae* by microarray hybridization. *Mol Biol* 1998;9:3273–97.
13. Brown PO, Botstein D. Exploring the new world of the genome with DNA microarrays. *Nat Genet* 1999;21:33.
14. Roberts CJ, Nelson B, Marton MJ, Stoughton R, Meyer MR, Bennett HA, et al. Signaling and circuitry of multiple MAPK pathways revealed by a matrix of global gene expression profiles. *Science* 2000;287:873–80.
15. Jelinsky SA, Estep P, Church GM, Samson LD. Regulatory networks revealed by transcriptional profiling of damaged *Saccharomyces cerevisiae* cells: Rpn4 links base excision repair with proteasomes. *Mol Cell Biol* 2000;20(21):8157–67.
16. Schena M, Shalon D, Davis RW, Brown PO. Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science* 1995;270:467–70.

17. DeRisi J, Penland L, Brown PO, Bittner ML, Meltzer PS, Ray M, et al. Use of a cDNA microarray to analyse gene expression patterns in human cancer. *Nat Genet* 1996;14:457–60.
18. Pollack JR, Perou CM, Alizadeh AA, Eisen MB, Pergamenschikov A, Williams CF, et al. Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *Nat Genet* 1999;23:41–46.
19. Stephan DA, Chen Y, Jiang Y, Malechek L, Gu JZ, Robbins CM, et al. Positional cloning utilizing genomic DNA microarrays: the Niemann-Pick type C gene as a model system. *Mol Genet Metab* 2000;70:10–18.
20. Hughes TR, Roberts CJ, Dai H, Jones AR, Meyer MR, Slade D, et al. Widespread aneuploidy revealed by DNA microarray expression profiling. *Nat Genet* 2000;25(3):333–7.
21. Ren B, Robert F, Wyrick JJ, Aparicio O, Jennings EG, Simon I, et al. Genome-wide location and function of DNA binding proteins. *Science* 2000;290:2306–9.
22. Ren B, Cam H, Takahashi Y, Volkert T, Terragni J, Young RA, et al. E2F integrates cell cycle progression with DNA repair, replication, and G(2)/M checkpoints. *Genes Dev* 2002;16:245–56.
23. Schaeffer AJ, Chung J, Heretis K, Wong A, Ledbetter DH, Martin CL. Comparative genomic hybridization-array analysis enhances the detection of aneuploidies and submicroscopic imbalances in spontaneous miscarriages. *Am J Hum Genet* 2004;74:1168–74.
24. Vissers LE, deVries BB, Osoegawa K, Janssen IM, Feuth T, Choy CO, et al. Array-based comparative genomic hybridization for the genomewide detection of submicroscopic chromosomal abnormalities. *Am J Hum Genet* 2003;73(6):1261–70.
25. Shaw-Smith C, Redon R, Rickman L, Rio M, Willatt L, Fiegler H, et al. Microarray based comparative genomic hybridisation (array-CGH) detects submicroscopic chromosomal deletions and duplications in patients with learning disability/mental retardation and dysmorphic features. *J Med Genet* 2004;41(4):241–8.
26. National Coalition for Health Professional Education in Genetics (US). Core competencies in genetics essential for all health-care professionals. Lutherville (MD): NCHPEG; July 2003 (Copyright 2001).