The future is now for rare genetic diseases

We agree with the cautionary note sounded by Roger Collier with respect to the hype surrounding genomic medicine.[1] In most cases a careful medical and family history combined with a thorough physical examination has as much, and very likely more, clinical prognostic power than does a complete genome sequence. There is, however, one area that we believe even now is delivering on the promise of modern genomics — the oft-neglected realm of orphan (rare) disease.

These individually rare but collectively frequent disorders affect an estimated 1 in 12 Canadians.[2] Although the genetic etiology of the significant majority of rare disorders is still unknown, the advent of next-generation DNA sequencing is resulting in the identification of rare and ultra-rare disease genes at an ever-increasing rate. This accelerating pace of discovery is best exemplified by the internationally leading Canadian FORGE (Finding of Rare Disease Genes) project, which in its first year alone had identified genes for over 50 rare disorders, affecting thousands of families.[3]

One estimate is that within a decade the clinical and biological impact of mutations in a third of all human genes shall be known,[4] truly a remarkable wealth of pathogenic knowledge that will profoundly affect our understanding of human biology at a molecular level. Moreover, given the shared phenotypic overlap with more common disorders, insight into these latter conditions might also be forthcoming.

Clinical impact is equally important. Patients might no longer be consigned to costly and often fruitless diagnostic odysseys while confronting an unknown future. Disease gene identification could bring diagnostic clarity (obviating extensive and expensive testing), suggest chance of recurrence within the family and define future clinical course and optimal medical management. Translational research for "common" rare diseases, such as Duchenne muscular dystrophy, spinal muscular atrophy and cystic fibrosis, has led to some thought regarding the generalized formulation to therapeutic approaches for the thousands of the other rare conditions.[5] Although the promise of genomic medicine lies ahead for complex disorders, the future is now for rare genetic diseases.

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The 5A model for the management of obesity

In their *CMAJ* article "Managing obesity in adults in primary care,"[1] Plourde and Prud'homme propose using the 5A model for the management of obesity. Recently, the Canadian Obesity Network launched a set of tools based on the 5A model, which specifically addresses the needs of practitioners in primary care.[2]

The tools are based on extensive research involving primary care practitioners, obesity experts and patients, and consist of the following steps (slightly different in some aspects from the 5A model presented by Plourde and Prud'homme):

- Ask for permission to discuss weight and explore readiness
- Assess obesity-related risks and "root causes" of obesity
- Advise on health risks and treatment options
- Agree on health outcomes and behavioural goals
- Assist in accessing appropriate resources and providers and arrange follow-up.

The development of these resources was funded through the Canadian Public Health Agency and the Canadian Institutes of Health Research. Toolkits can be obtained through the Canadian Obesity Network (www.obesitynetwork.ca).

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The authors respond

Thank you for sharing this new information.[1] The 5A model for the management of obesity recently launched by the Canadian Obesity Network (CON) is an excellent resource that could be added to "Box 5: Resources for physicians and patients" of our article.

As mentioned by Dr. Sharma, there are minor differences to the "classic" 5As described in our article and those of CON. In the 5A model we presented, we mentioned that Ask/Assess can be used interchangeably. Because we aimed to discuss counselling on dietary and physical activity interventions, we decided not to include Ask.

However, not to ignore the importance of Ask, a case report[2] referenced in Box 3 describes the application of the components of motivational interviewing, including agenda setting, which involves "asking" permission to discuss the issue of interest, and explores readiness for change and strategies to modify barriers to weight management.

Another minor difference with CON's 5A model is about assessing for obesity-related risks and "root causes"

of weight gain. Under Assess, we specified to conduct clinical and laboratory investigations for comorbidities and to treat comorbidities and other health risks, if present. Also, in the introduction section, we mentioned multiple reasons for obesity, but we decided to limit our discussion to the principal cause being a positive energy balance secondary to an excess intake of calories and/or with low energy expenditure. More information about other "root causes" of obesity and how they should be approached is available.[3]

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Contrasting coroners

The research article by Walter and colleagues[1] highlights the work of coroners, but the results are not generalizable to Canada, or Ontario, in particular.

The authors did not attempt to analyze factors predicting coroners' decisions outside of Australia. In contrast, coroners in Australia are barristers, whereas coroners in Ontario are physicians. This is one reason why Ontario's inquest data differ significantly from those of Walter and colleagues.[1]

Ontario conducts fewer inquests than Australia per year and per capita. Ontario's system reviews all investigated deaths for potential inquest, guided by a structured review process and the Ontario Coroners Act. A discretionary inquest may be called where a coroner's jury may be able to render a verdict that could not be reached by investigation alone; where the jury could make previously unappreciated recommendations; and/or where the public interest may be served via a public hearing. However, the relative merits must be carefully considered in each case.

The Office of the Chief Coroner[2] keeps data on a number of aspects of inquests. Each year from 2000 to 2009, an average of 70 inquests were held in Ontario (59 mandatory and 11 discretionary inquests), providing an average of 493 recommendations per year (unpublished data). In contrast to Australia, Ontario conducts few inquests into pediatric deaths or those due to complications of medical care. Lay juries are challenged by complex medical issues. Hence, such matters are best dealt with by multidisciplinary expert review committees, individual case-based recommendations or regional coroner reviews.

Physician coroners allow for more efficient inquests by applying medical knowledge. Death investigation, in our view, is and ought to be based in medicine supplemented by the law.

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The authors respond

McCallum and colleagues point out that coroners in Ontario are physicians, whereas those in Australia are lawyers.[1] Our understanding is that the physician-only model operates in some Canadian provinces (e.g., Alberta, Manitoba and Ontario) but not in others (e.g., Quebec, British Columbia and Saskatchewan). In any case, we would readily concede that specific findings from our analysis of characteristics of deaths that are disproportionately more and less likely to reach inquest in Australia[2] may not be directly generalizable to Canada.

The more important issue, however, is whether the questions about coronial practice our research poses have salience in Canada and other international settings. We believe they do. As McCallum and coauthors indicate, decisions by Ontarian coroners about which cases to take to inquest are the product of a series of subjective determinations.[1] Understanding what body of public death investigations those determinations produce, and whether and how it differs from the broader body of deaths coroners investigate, is worthwhile. Inquests are both a springboard for recommendations and an important influence on the public's understanding of untimely death. Indeed, subjecting coroners' cases to the kind of epidemiologic analysis our paper presents may be especially useful in a jurisdiction like Ontario, where inquest rates are relatively low and the vetting process is extremely selective.

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Letters to the editor

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