ageing of the population per se, that adds to pressure on health services and makes it harder to find the time for doing anything other than following treatment guidelines and meeting performance targets.

Yet feeling cared for is something that patients have always valued. In *A Fortunate Man*, an exploration of a general practitioner working in a deprived rural community in the 1960s, John Berger concluded that the physician was much valued by his patients not because of his clinical acumen, but because of his capacity to accompany people in their fear and anxiety.[10] This brings us to the key issue of trust. To feel cared for is to trust. But trust is not just a quality of the relationship between a doctor and a patient. It is also a crucial dimension of a much broader set of relationships that citizens have with organisations, institutions, and government that is essential for societies to be able to function.[11]

The NHS is seen by many as a key national institution of value and trust, indeed, is emblematic of the sort of society we wish to live in. More attention needs to be given to the experience people have when they interact with it.[12] Doing this cannot be achieved by endlessly pressing for greater efficiencies, which assumes all things of importance can be monetised. A better definition is needed of the value people place in the services that are established to treat and support the sick and the frail. Developing this definition will require a rethink within the medical and caring professions about how the human dimension of care can become more central to training and practice, and deliberation of how far medical innovation should be defined purely in terms of technological and pharmacological advance. However, none of these changes will be facilitated if the UK Government continues in the misguided belief that improving the value and trustworthiness of the NHS will be achieved by promoting distrust in the foundations of the institution and those who work in it.

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Glaucoma treatment: by the highest level of evidence

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50 years ago, ophthalmologists thought glaucoma and increased intraocular pressure to be synonymous.[1] In 1958, Wolfgang Leydhecker defined healthy limits for intraocular pressure[1] and patients with intraocular pressure of 21 mm Hg or higher received a diagnosis of glaucoma, irrespective of whether there were any signs of glaucomatous damage. They were given intraocular-pressure-lowering eye drops, and were told to use these drops three to four times a day or they would go blind. Patients with pressures of 20 mm Hg or lower were told that they did not have glaucoma.

The problem was that increased intraocular pressure and glaucoma are not synonymous. The first epidemiological study of glaucoma, done in Wales, UK in the 1960s, showed that many patients with glaucoma had intraocular pressure measurements within Leydhecker's healthy range; these patients were said to have normal-tension glaucoma.[2] These findings have been confirmed in dozens of other epidemiological studies, and it is now accepted that about half of all patients with glaucoma have normal-tension glaucoma—a proportion as high as 90% in Japan.[3] Equally confusingly, there were many

patients with pressures of 21 mm Hg or higher without glaucomatous damage, and when these patients were monitored without treatment for up to 20 years, most of them developed no signs of glaucomatous damage.[4]

Thus, ophthalmologists realised that the relation between increased intraocular pressure and glaucoma was not clear, which led to doubts about the efficacy of intraocular-pressure-lowering therapy. Because this uncertainty was an obstacle to clinical decision making and to allocation of sufficient resources for glaucoma care, clinical studies were needed. The problem was first addressed in four randomised clinical trials in the 1980s[5–8] that investigated whether a reduction of intraocular pressure in patients with increased pressure in the absence of glaucomatous damage (ocular hypertension) could reduce the incidence of glaucoma damage. Results were inconclusive,[5–8] and a 1989 report commissioned by the US Congress concluded that there was no proof that lowering of intraocular pressure reduced glaucomatous damage. Investigators then started two randomised controlled studies of patients with manifest glaucoma. The Collaborative Normal-Tension Glaucoma Study (CNTGS) enrolled only patients with normal-tension glaucoma, whereas the Early Manifest Glaucoma Trial (EMGT) studied patients with glaucoma who had normal and increased pressures; both trials compared pressure-lowering treatment with no treatment. The intention-to-treat analysis in CNGTS did not report significant effects, but after correction for the increased incidence of cataract in the treated group, the researchers reported positive treatment effects.[9] Findings from EMGT showed that pressure lowering had positive effects, irrespective of patients' initial intraocular pressures.[10]

In *The Lancet*, David Garway-Heath and colleagues[11] report results of the United Kingdom Glaucoma Treatment Study (UKGTS), a randomised clinical trial to investigate the effects of intraocular pressure lowering in glaucoma patients with healthy pressures. UKGTS involved ten centres in the UK, in which 516 patients were randomly assigned. In some ways, UKGTS was modelled on the EMGT—eg, the original primary outcome (which was later amended), but the two studies also differed in several respects. First, UKGTS was placebo controlled and EMGT was not. Second, UKGTS used monotherapy in the treatment group—prostaglandin analogue eye drops (latanoprost 0·005%), the most commonly used antiglaucoma therapy in high-income countries. The authors also aimed to use a study design from which conclusions could be drawn in a relatively short time—patients were followed up for only 2 years. To achieve this, 11 visual field tests were obtained during this period, since it is well known that identification of visual field progression or measurement of rate of progression needs several field tests, and that the time needed to identify progression strongly depends on the frequency of testing.


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Garway-Heath and colleagues' study[11] is important in many ways, perhaps most importantly because it is the second to show the positive treatment effects of intraocular pressure reduction in manifest glaucoma. For the highest level of medical evidence, more than one study is usually required and this has been absent in the area until now. Since modern glaucoma treatment is based on reduction of intraocular pressure, and because glaucoma management uses about 25% of all ophthalmology resources, this is a fundamental issue in ophthalmic care. That the study was placebo controlled is a further strength.

The magnitude of treatment effects is also important. The intraocular pressure difference between the treated and the placebo groups after 24 months was slight (2·9 mm Hg), due to the fact that untreated pressures at study entry were quite low. Intraocular-pressure-reducing drugs produce much smaller pressure reductions in eyes that start with low pressures than in eyes in which pressure is high. Still, the risk of progression was substantially lower in the treated group than in the group receiving placebo drops (adjusted hazard ratio [HR] 0·44 [95% CI 0·28–0·69]). From this HR, the risk reduction could be about 19% per mm Hg, confirming results from the EMGT and Canadian Glaucoma Study, and showing that intraocular pressure reduction is highly effective, and that every mm of pressure counts.[12,13] These results should motivate careful clinical follow-up and monitoring of disease progression in patients with glaucoma, and should also serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.

It is important that Garway-Heath and colleagues[11] documented very significant treatment effects after only 24 months; in fact, the first differences were seen after 12 months (adjusted HR 0·47; 95% CI 0·23–0·95). Certainly, the UKGTS took a lot longer than 2 years to complete, but only because recruitment took several years. Measurement of glaucomatous progression with visual

field status is the gold standard, and visual field sensitivity is also important to patients. Nevertheless, in recent years some researchers have stated that studies using visual field endpoints take too long, and that it is too difficult to assess the effects of new drugs or other treatments. Garway-Heath and colleagues clearly show that this view is pessimistic, and that, with frequent testing with widely available clinical instruments, important studies can be completed within a very reasonable time. I expect this to be the first of a series of papers reporting UKGTS results; additional findings will be reported in future, notably those that compare the results obtained with visual field testing with those of ophthalmic image analysis.

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I consult for Carl Zeiss Meditec and Allergan, and have received honoraria for speaking from Allergan, Merck Sharp & Dohme, and Santen.

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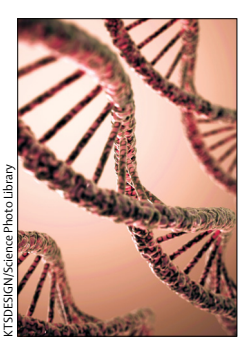
Developmental disorders: deciphering exomes on a grand scale



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Completion of the first reference human genomes, now nearly 15 years ago, was a mammoth achievement. Expectations were high and predictions of revolutionary effects on science, and medical practice in particular, justifiable. However, we had to wait another 5 years to read individual genomes affordably, and another 5 years before we started to use the information to address the genetics of rare human diseases. The past 5 years have been spectacular, with almost daily novel gene discoveries, not only for rare mendelian diseases but also for complex and multifactorial disorders. With the collected knowledge from the tens of thousands of individuals' exomes and genomes available, and the thousands now being generated daily worldwide, we have come to realise the vastness of individually rare genetic variation in human genomes. We have learned much about the frequency of de-novo mutations and their relevance to disease. In particular, study of neurodevelopmental diseases such as intellectual disability,[1] autism,[2] epilepsy,[3] and schizophrenia[4] has benefited, together with that of cancers.[5] Several excellent how-to exome guides, most of which tackle the difficult tasks of sorting pathogenic from non-pathogenic DNA and protein variants, using disease inheritance models or a de-novo mutation hypothesis combined with an appropriate selection of bioinformatics tools and laboratory validation methods, have been proposed.[6–8] With these approaches, genome-scale sequencing technologies are finally entering medical practice more broadly as unifying tests for diagnosis of genetic disorders.

In *The Lancet,* Caroline Wright and colleagues[9] report a robust and scalable diagnostic whole exome sequencing workflow, and its practical use when applied to data for 1133 patients collected as part of the Deciphering Developmental Disorders (DDD) study in the UK. The report outlines the processes taken from recruitment, data management, and processing, the choices made to do both automatic and manual variant filtering of around 80 000 variants per individual, and the framework for reporting results. Great care has been taken at every