

Skin cancer, and some limitations on how we innovate and practice medicine

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Summary

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Successfully delivering medical care and acquiring and disseminating the new knowledge that underpins clinical advance requires dealing with a number of both theoretical and organizational issues that may impede progress. Firstly, we have to move beyond the idea that biology and medicine are synonymous, and realize that tropes such as 'bench to bedside' or 'translational' frequently do not capture the way medical advance occurs. Medicine is more engineering than science, and the constraints imposed by society and economics, as well as historical models of working, may all delay improvements in healthcare delivery. Secondly, the generation of new ideas is influenced by the social organization and financial underpinning of science. Comparisons with other areas of science and technology suggest that medical science is dysfunctional and lacking in genuine innovation, particularly when cost is factored in as a key denominator. There are reasons to believe that matters are getting worse, and that the climate for revolutionary discovery is less supportive in both academia and industry than it was in the mid-to-late twentieth century. Thirdly, healthcare delivery is subject to a number of factors that limit cheap and effective care. These include payment systems that encourage unnecessary care, self-interest by medical guilds and insurers, and regulators that seek to limit new ways of working. Finally, there is also a striking failure to study and understand medical competence, how we educate doctors and other clinicians, and how technology might help to reduce costs.

Here are two opening statements about skin cancer. We understand human skin cancer better than we understand almost any other common human cancer, and most of the quantitative information that currently guides clinical behaviour has come from the clinic rather than from cancer model systems. Think of the century-old observations on body-site distribution and sun exposure. Think of the covariation between skin colour, skin phenotype and cancer incidence, and hence of the protective role of melanin against ultraviolet radiation (UVR). Think of the relation between cancer incidence, latitude and human migration. But then supplement these clinical observations with two triumphs of molecular biology: the elucidation of the genetic basis for skin cancer in xeroderma pigmentosa, and the identification of the UVR-related mutational spectra of common skin cancers.

Of course, we do not know enough. The preceding statements concern causation rather than treatment. And medicine is more engineering than science, focused on knowing enough to act effectively rather than an endless pursuit of nature for its own sake. If we know we can stop most cases of lung cancer by avoiding cigarettes, our sense of the need

for yet more mechanistic enquiry is somewhat dulled. Insight into causation is important, but without the ability to intervene, our knowledge is incomplete.

Biology is not sufficient

When I was immersed in the study of the genetics of human pigmentation, I felt uneasy about the hype that surrounded so much modern genetics. I used the following phrase: genetics is a great way of doing biology but biology is not synonymous with medicine.¹ Depending on your background, you may view this phrase as trite and unnecessary, or, alternatively, provocative. It is very easy given the rate of advance in biology to imagine that what older clinicians would call clinical practice would form an ever smaller part of our collective professional endeavour. Sometimes it is the name we choose that belies our prejudices.¹ Many of my colleagues now work in departments of 'dermatological science', rather than departments of dermatology. They are 'molecular dermatologists', not, it seems, mere practitioners of dermatology.¹ In this vision, as we acquire more and more biological knowledge,

the resulting areas of ignorance and uncertainty about clinical practice shrink. But I do not think this is a useful way to view medical practice. Rather, as the amount of biomedical knowledge increases, so does the domain of clinical practice grow ever larger. Our biomedical knowledge does not replace or squeeze out other knowledge, rather the vessel that is clinical practice is also expanding. So, what is this other stuff that I demarcate as not being biomedical knowledge but which I claim is growing?

Frank Davidoff, in a telling metaphor, likens some of this stuff to physicists' dark matter.² Physicists believe that most of the universe is made up of dark matter, material that they know exists but about which they know very little. Talking about competence – that is how good doctors are at their job – Davidoff likens medical competence to dark matter: it makes up most of our working knowledge but we know little about it. Atul Gawande comes at the problem from a slightly different direction, arguing that science has now filled in so much knowledge that ineptitude is as much our struggle as ignorance (echoing an earlier argument of Gorovitz and MacIntyre).^{3,4}

There is a phrase used by engineers that goes roughly as follows: physics was made by God but to engineer is human. Engineers have, of course, to be cognisant of the laws of nature, but that is only part of what they need to know in order to build artefacts. This applies to medicine, too. Science may tell us about how the natural world works but we want more than that because we also have to know how science and society work. We want to intervene, and the test of our knowledge is how well we can do this in the social and economic systems we inhabit. UVR causes most skin cancer, but if the patient in front of us already has a thick nodular melanoma, we have to ask the following question: was it inevitable that they would present when they did, and what can we do for them now? But the answers to these questions do not just depend on biology. Medical engineers not only have to talk the language of molecules, but also the language of health insurers. Furthermore, medical engineers also have to know how to engineer their own cultures of discovery, along the way.

Limits to prediction, and the play of the dice

Many years ago my colleagues and I published the first two papers showing that mutations of the melanocortin 1 receptor (MC1R) could be used to predict who might get either melanoma or nonmelanoma skin cancer.^{5,6} If some could dissent from the then all embracing hype about gene therapy, then at least the idea that we could stratify people and tailor advice to particular groups seemed a consolation. People would scour twin studies, justifying the search for genes that underpin heritability, all with the goal of claiming how clinically useful this new-found information would be. This was a conceit that has now spread into much of the rest of medicine. What always struck me was how low the heritability scores were for most cancers. It has been said before: the most interesting thing about most identical twin pairs is what is different between them.

If you are not trying to identify particular genes, there is, of course, another way into this conundrum. Imagine a pair of genetically cloned humans who, by virtue of your strict experimental design, have shared an identical environment. If we had access to such 'clones raised in cloned environments' what could we learn? Well, we do have access to such individuals, they are called normal patients. A patient with an index tumour diagnosed and treated on day X , is genetically identical and shares a largely common environment with the same individual on day $X + 1$. As time goes on, the experiment runs. Studies of second tumours are, in effect, studies on cloned patients who share an almost identical environment.

Imagine a 60-year-old patient with melanoma who, despite having the same genetic makeup for the rest of her life, and an identical historical environment, is still much more likely never to have to have a future melanoma than to have one.⁷ Same genes; same environment. What this means is that chance – bad luck – plays a critical role in determining our fate. Most variance, in the statistical sense, remains unexplained. If we choose high-risk populations – think of the over 80s in Queensland – most of the variance will still be unexplained.⁷ Why is this important? Simply, that if, as many now admit, gene therapy was overhyped over a decade ago, we are currently in another hype cycle of personalized or individualized medicine that may also disappoint more than it changes practice. Reliable cure still has attractions over the uncertainty of some future state.

Limits to developing new ideas

Given best available care, if we are going to cure patients we cannot currently cure, we are going to do so on the basis of new knowledge. In the two areas I have researched, namely genetics on the one hand, and, more recently, informatics on the other, there is, I think, a consensus that the environment for bold thinking has become worse.^{8–10} The statement 'either do something very beautiful or very useful' was said to be the informal motto of Bell Labs.¹¹ For the two most widely accepted institutional icons of scientific discovery in the mid- and late twentieth century, Bell Labs in the U.S.A. and the Laboratory of Molecular Biology in the U.K., beauty and utility so often went together. Most of the power of modern genetics and most of the power of modern computing we owe to young people 'looking for something beautiful'. The sense of play was not an optional bolt-on but more the muse of intellectual revolution. Michael Eisen, the U.S. geneticist, in his blog (<http://www.michaeliseisen.org/blog/>), has suggested (and I paraphrase) that while there has never been a better time to do science, there has never been a worse time to be a scientist. If people spend a large part of their working life scratching around for funds, or trying to second guess what those with money to give say, or reach middle age before getting a chance to make their own mistakes, we short change our future selves. A steady stream of commentators from the centre ground of the academy have pointed out that academic science is, if not broken, sick.^{12–15}

If that is academic science, what of industry? Most people are aware of Moore's law, named after the co-founder of Intel, Gordon Moore. The law says that the number of transistors in an integrated circuit doubles every 2 years. Over the last 50 years computing power has increased exponentially, and the price per unit calculation has also gone down exponentially.

Few are aware of a more dismal counterpart in medicine: room's law – Moore's law backwards.¹⁶ This apt moniker, first used by Jack Scannell and colleagues, reminds us that during the same time that Moore's law was revolutionizing not only the world of computing, but also the world we live in, the cost of developing new drugs had increased (not decreased) over 100-fold. As Scannell and colleagues observe, over the very same period that Moore's law has applied, we have become technically much more efficient: we can sequence DNA a billion times faster, synthesize more chemical entities and so on. But still the failure rate in the clinic is largely unchanged.

There are lots of possible explanations for this state of affairs, which Scannell *et al.* critically appraise.¹⁶ Too much regulation is one favourite. Or that the low-hanging fruit has been taken. Or the obsession with magic bullets rather than magic shotguns ('dirty drugs are best'). And the industrialization of clinical research. But the one I like best is the 'Better than the Beatles' metaphor. Imagine how hard it would be to achieve commercial success with a new pop song given the following: any new song has to be better than every Beatles song; the entire Beatles catalogue was available for free; and people do not get bored listening to old Beatles records. Think generics. It is not a comfortable thought.

Limits to delivery

David Margolis describes how when he was at college in the early 1980s, wet bench science, including genetics, immunology and so on, promised to revolutionize medicine.¹⁷ By contrast, writing in 1998, he observed:¹⁷ 'it seems to me as a clinician that no change has been as dramatic as the changing landscape of who is primarily responsible for patient care and who pays the bill'.

Medicine is being industrialized,¹⁸ and one of the most striking things to say about that process is that few people want to discuss it or openly challenge the argument, except by the default option of short-term gaming of the system or sticking their heads in the sand. Or retiring.

At the turn of the twentieth century one in three healthcare workers were doctors; now the figure is one in 16. In the 1950s there 10–12 categories of healthcare professionals.¹⁹ Today, there are 220 categories. After the Second World War there were 6–8 specialties in medicine. Today there are more than 100. Much of medicine is run on a corner shop, small-group basis. For some areas of medicine that may make sense.²⁰ For skin cancer, I and others have argued, it does not.²¹ Skin cancer 'factories' in which a large number of non-physicians work under the guidance of experienced physicians

is surely worth moving towards in larger cities. We have become used to paralegals replacing many jobs once done by lawyers;²² we know that hygienists can take over a significant amount of work that previously was done by dentists. Our problem, as one dentist pointed out to me, is that dentists are overqualified for 70% of what they do, and underqualified for much of the remaining 30%. The same goes for skin cancer, I suggest.

In the U.K. and many other countries there is an epidemic of naevus removal. A relative of mine (in another country, I should say) recently saw his private 'item of service physician' about a haemangioma on his head. It was misdiagnosed as a melanocytic naevus. Furthermore, he was advised that a dozen or more normal melanocytic naevi over the rest of his body also needed to be removed. No doubt, 3-monthly checks for the scars would have been advised.

Large clinical centres in some clinical domains allow better collation of data, and quality control, and allow providers to bear the costs of unnecessary surgery.²⁰ All that we know about clinical expertise is that continued practice, high-level exposure and feedback are critical.²³ Nobody believes that an office-based 'general' radiologist should report a few mammograms a week: ditto for seeing patients with skin cancer. Nobody should be deciding on naevus removal unless they are seeing a high volume of normal naevi (and melanomas). Yet, the literature suggests large differences in clinical decision making between physicians, costs that are not borne by the physician, but by the patient or the insurer.²⁴ You get sentinel lymph node biopsy here but not 50 miles down the road. You get surveillance here but not there. As the Dartmouth group have argued,²⁴ treatments and behaviours that are at best marginal are driving large amounts of healthcare spending. This cannot go on.

Medical education and training

You cannot dissociate this concern about medical competence from the way we think about training, both at undergraduate and postgraduate level.²⁵ The only thing that outpaces healthcare costs is the cost of higher education in North America and, more recently, in England.²⁶ Current U.K. funding models of higher education are unsustainable. Sadly, the leaders of many universities resemble the executives of the record labels who insisted that people would continue to pay £15 for a CD, totally oblivious to the fact that Steve Jobs was dismantling their industry and their business model.²⁶

If I want to train in medicine I could choose a 3-year degree in some places, whereas in others it takes 6 years.^{25,27} The European Union has rules about medical certification based on – you guessed it – not assessment of knowledge or competence but time spent. A bit like a prison sentence, only without any possibility of parole. If you want to train as a dermatologist, the U.K. Royal Colleges want you to believe that 3 or 4 years of internal medicine is essential or, furthermore, that you can only be a dermatologist if you practice as an internist at the same time. Move across the channel to

mainland Europe and all is different. Everywhere you look you see evidence of dysfunctional systems in which medical guilds, insurers or governments are seeking to resist change, acting so as to increase directly the cost of care, and, indirectly, to limit access to healthcare.²⁷

If you want an example of the power of retooling and reorganization of healthcare staff, look at dermatological surgery. If anybody wanted an example of Clayton Christensen's much applauded (and abused) term disruptive innovation,²⁸ here it is – probably the largest change in clinical dermatology in my professional lifetime. This system change in the organization of care can offer enormous savings in terms of matching surgical and diagnostic skill. Alternatively, it can metastasize into something far worse, in which the risks from banal lesions are exaggerated as a pretext for larger fees. Perhaps it will be just organic growth, but we need to think hard about whether the tie between skin cancer and dermatology needs to be broken, and whether we could shorten and improve training by the creation of a separate specialty. You may disagree, but we should be having the conversation. We have to think skin cancer, not dermatology, not plastic surgery and so on. If people want to download songs rather than buy whole albums maybe we, too, need to alter our business model.

Finally, nobody, in my opinion, has melded the possibility of digital technology with diagnosis in such a way as to both improve and cheapen care, except in very niche areas. There are a couple of issues here. Fully automated diagnosis based on computer vision is hard. With language processing, brute-force statistical approaches have yielded game-changing insights into the nature of the problem, but scale is more easily achievable in this area. My own work on computer vision has worked with datasets of ~ 6000 lesions, and whereas we can achieve diagnostic accuracy scores of close to 70%, this is nowhere near sufficient.^{29,30} My guess is that if we are going to brute force it, we will need training sets at least several orders of magnitude larger, something that might only be practical when we have a fully digital workflow. A digital workflow is, of course, important for other reasons: like the phone in your pocket betraying your movement, a digital workflow allows review of clinical decision making and whether reimbursement is made to a provider.

Conclusion

I started this article with the claim that many of the key insights into skin cancer have come from the clinic. The clinic also remains the terrain on which all innovation must be judged. We revere the names of Janssen, Hitchings, Black and Elion simply because they were, indeed, geniuses, introducing revolutionary therapies.^{15,31} And this revolution was labelled as such based on the impact in the clinic – not by a corporate or university press office. Skin cancer, just like much modern medicine, faces at least two challenges. The first is the tendency for both the academy and pharma to try and achieve success by redefining what success means. For instance, to imagine that risk stratification is the same as cure: it isn't. The

latter is much harder. Or to redefine trivial dysplastic lesions as cancer. The second is a reluctance to redraw the boundaries of medicine for an age in which biomedical knowledge is only one part of the mix. The proper study of medicine is not just disease, but medicine itself, and that must mean the study of how doctors practice, and how new ideas and society influence what they do.

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