

Speaking for Myself

Mini's Spink

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Man with all his noble qualities ... still bears in his bodily frame the indelible stamp of his lowly origin.

From: *The Descent of Man* (1871), closing words
By: Charles Darwin (1809–82), English natural historian

My niece weighed 1.8 kg at birth. We called her Mini because she was so tiny. And she became 'Mini' for life. On most fronts, she caught up quickly. She has now grown taller than I, at 5'9" she has a stunning personality, but we still call her 'Mini'.

She sent me an SMS when she passed her MB,BS: 'Uncle, beware, I am now "licensed to kill".' I was extremely proud of her. In our large family, she was the only one after me to have opted and qualified for medical college. I thought of her as the inheritor of the 'priceless pearls of wisdom' that I have accumulated over the past 40-odd years.

My elation about Mini qualifying MB,BS was dampened a bit when she announced, 'Uncle, the stress of a clinical subject is not for me. I am keen on research.'

I tried to persuade her, 'As long as your subjects for research are human, you will have to be a clinician!' But she did not agree.

Mini was bright and always got what she wanted. She joined as a Research Associate at the Department of Genetics of Sir Naroji Hospital (SNH) in our city. It is a reputed private hospital which also runs several postgraduate medical courses. Her subject of interest was molecular genetics and she soon registered for her PhD with a local university.

Her guide was a retired professor from a famous government medical institute, who was pursuing her second innings at SNH and was known for her work in this field.

During her frequent 'local guardian visits' to my house, Mini often showed her obsession with her work, 'Uncle, I love the lab we work in. We have five technicians. I am supposed to supervise them as I learn the basics from them.'

On another day she chirped, 'Today, I did my first independent real time-polymerase chain reaction! It's amazing how accurate this test is. We can pick up even a single nucleic acid molecule in a sample.' I smiled as I knew it was an exaggeration.

Over the next few months her confidence and faith in her subject soared sky high and I loved watching this transformation. One day she talked about Renee, who was her young but most intelligent lab technician, and was engaged to be married in a couple of months. 'Her fiancé, Ravi is working at a BPO. He often brings *samosas* for our team; this is a bribe to take Renee away a few minutes before closing time. I am gaining weight because of their love-affair!'

A few days later she came home in a pensive mood, 'Uncle, what do you know about *SPINK-1*?'

This is what I disliked about her. She was always testing me.

My knowledge about this unexpected term was hazy. 'Isn't it one of the enzymes in the pancreas? But, why did you ask that?'

'You are right, Uncle! *SPINK-1* stands for 'serine protease inhibitor, Kazal type 1.' It prevents premature activation of another enzyme—*trypsin*, and thereby protects against pancreatitis.'

'That does not answer my question. Why is this *SPINK* making you so glum?' I asked.

She answered like an expert. 'Oh, one of the postgraduate trainees (PG) at SNH is doing a PhD thesis on *SPINK-1* gene mutations and tropical pancreatitis. Some of the mutations at this gene site, i.e. *N34S* mutation, are supposed to predispose a person to pancreatitis.'^{1,2}

I now remembered having read about it. Normal *SPINK-1* was an inhibitor for the master detonator of pancreatitis (*trypsin*) within normal acinar cells. The mutated *SPINK-1* failed in this inhibition, leading to *in situ* activation of *trypsin*.

Then she dropped the bombshell, 'Renee's fiancé Ravi has it, and everyone in our lab is depressed.'

'Has Ravi developed pancreatitis?' I was curious.

Her reply was matter of fact. 'No, Ravi has *SPINK-1* gene mutation *N34S*!'

'But why did he get that test done?' I was now confused.

'It is a long story.' She hastened to explain, 'You see, Ravi's blood was lying with us for some other routine health check-up tests. And this PG, whose thesis topic is *SPINK-1* gene mutations, could not find enough normal controls for his project. He persuaded Renee to get some samples from people who come for routine check-ups and had no known disease. Renee did a favour to this PG and ran her fiancé's blood sample as control. It turned out to be positive.'

'What did you do?' I looked at her with disbelief.

'Renee told Ravi. And now Ravi and Renee are both crying. Ravi feels if he is going to develop such a dreadful disease, then he would not like to spoil Renee's life. The marriage may be off. Tell me, Uncle, can pancreatitis be cured?'

'But why did Renee tell Ravi?' I asked.

'They are in love and don't hide anything from each other. And this is a major thing!'

I could not stop myself, 'Mini! This is terrible! Being the supervisor of the lab and a doctor, you are responsible for this disaster.'

She appeared shocked, 'Where do I come in? I haven't given him his genes, his parents did.'

'Oh, he was quite happy with his genes till you decided to give him information he did not ask for. This is a sure recipe for disaster.'

'I did not give him any information! His fiancée did!'

'No, Mini, the lab under your supervision did. As a doctor you may have crossed ethical limits.'

'You are pinning everything on me; I did not even know when the test was done.'

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'In that case it is your failure as a supervisor! You cannot shy away from it.'

Tears welled up in her eyes. 'Uncle, you are deliberately trying to be nasty with me. As it is, I'm feeling bad for Renee's predicament.'

I walked up to the fridge and got her a glass of chilled water. 'We need to seriously talk about this issue. Tell me whenever you are ready for it,' I said.

'What is there to talk? I came home feeling sad for a colleague and here you are blaming me for a disaster.' She was still sobbing.

I decided to do so some more plain-speaking. 'Have you ever given your blood for testing?'

'Yes, many times. Even on the day I joined this lab, I was tested for HBsAg and was prescribed HBV vaccine.'

'Suppose, Renee walks up to you tomorrow and says, "Madam, I ran your blood as a control sample in one experiment, and you have tested positive for the BRCA1 gene. I've checked up on the net.^{3,4} You will now have to undergo bilateral mastectomy and bilateral oophorectomy!"⁵ How would you feel in that situation?'

'You are horrible, is all I can say.' She shouted and walked out of the room.

'I agree with her.' This was my wife who had overheard the last bit of our conversation. It was my wife's turn to do some plain-speaking. She told me explicitly how insensitive and useless I was when it came to talking to girls. She stomped off to console Mini.

Mini must have cried the whole afternoon, because her eyes were blood shot when she came out of her room after about two hours. She surprised me by saying, 'I am ready for a chat. Tell me, what should I do?'

I hesitated for a moment but decided to go on. 'I want to start from the very beginning. Do you remember what you said after passing MB,BS?'

'You mean that SMS about "licensed to kill"? It was just a joke! That is a James Bond tag line. Everyone says it without meaning anything,' she said.

'No, you said, "the stress of clinical subjects is not for me, I want to do research". Remember that?'

'Yes, I did. I hate this kind of situation.'

'Brace yourself, you cannot run away from being a clinician even when you are in the lab. You continue to affect people as clinicians do. When you touch human lives, you have to be ready to accept the stress that comes with it.'

'Uncle, drop your *I-told-you-so* attitude and tell me what to do.'

'You will know what to do if you realize where you have gone wrong.'

'Okay, tell me, to your heart's content!'

'First you do not test anyone for anything unless you have his or her consent.'

'Yes, I know about informed consent. But this was different. It was just a sample run as control.'

'Did you tell Ravi before running this test that—if positive, the result will have implications that could change his life?'

'You mean counselling as one is supposed to do for HIV testing? But the same is not required for every test.'

'Every test which can change a person's life needs to be treated the same way!'

'Does that mean I should inform all my subjects about every possible implication, however improbable it may be?'

'It is an ethical obligation, and even a legal requirement in many countries!⁶ The disclosure of risk can be dispensed with only in the event (i) if the patient is judgementally or psychologically

impaired (in this case, next of kin or the patient's proxy would need to be contacted and informed) or (ii) if the patient refuses to hear a recitation of the risks.'⁷

'If I was to explain all the potential risks of every possible test/intervention regardless of its likelihood, I will not have time to do any other work!'

'Well, your fear is valid.⁸ This is where the need for training in communication skills becomes important, which enables a doctor to effectively exchange information and give a sense of teaming with patients, their families, and professional associates.'⁷

'Then, Uncle, I am afraid, there can be no research. Why would a normal person come for being tested as a control?'

'It is for research workers like you to appeal to her/his altruistic nature. If you do not get normal controls, you cannot decide to treat human beings as you would test lab animals!'

'But there is something known as anonymous testing.'

'You are right. But in your case the test was not anonymous. Renee knew it was Ravi's sample and she even went on to tell him the result and implications—without even finding out if he is ready for it.'

'How does it matter? The truth has to be told.'

'Mini, remember! It is a person's right to know everything about himself, but it is not his duty to do so.'

'What does that mean?'

'It means a person may choose not to learn about the results of a particular test. In such a situation, the doctor should not force that knowledge on him. It is one of the basic principles of medical ethics, i.e. autonomy.'⁹

'But Uncle, I am still uncertain as to why would anyone get a test done and not want to know about the result?'

'Take me, for example. I may agree to get a test done because my wife is insisting or my niece is insisting or because it may be required by my doctor to do some fine tuning to my therapy.'

'But why not know the result?'

'Oh, I may feel that I am already overburdened with information. I might prefer to watch a comedy film rather than try to peer into 500 tests that my doctor orders for me, especially if the tests may contain bad news, interpreted on the basis of bad statistics. In any case, my doctor is being paid to look at those results and take decisions.'

'Okay, I accept that Renee made a mistake of testing that sample and was wrong in telling Ravi about the result. What should I do now?'

'First, you make sure a similar thing does not happen in your lab again.'

'Done! I will make sure.' She kept looking expectantly at me. I now had to deal with the more difficult part.

'The second thing is not to assume the mantle of an expert and talk to any patient on her/his illness unless you understand the topic well and unless you are the doctor-in-charge.'

'What do you mean?'

'Genetics may be your subject, but you are just learning. Remember that your words are going to affect a human being, who has feelings and emotions.'

'You are being vague. I have read all the basics of genetics.'

'Okay, let me tell you an anecdote I read recently.¹⁰ A lady was devastated when her paternity test (by DNA fingerprinting) was compared with her father's test and the result was found to be negative. It left her worrying about her mother's possible infidelity.'

'I would worry too! DNA fingerprinting is the ultimate test. It cannot be wrong!'

'Think again! There are plenty of reports about the fallacies of

these tests.^{11–13} And then there is the issue about “chimeras” in nature.^{14,15}

‘You mean chimera as in Greek mythology—the one with the head of a lion, body of a goat and tail of a serpent?’

‘I mean chimera, as in human beings with more than one genetic cell line! You see, it is easy for you as a student to categorically say that DNA fingerprinting is 100% accurate. You are almost right, but it does not help the person who is affected by one uncommon chance anomaly. Your statement may ruin his or her life.’

Her eyes suddenly lit up. ‘Are you suggesting that Ravi has one of these chance anomalies?’

‘You need to understand that Ravi is not devastated by the test result. It is your prognostication that has shattered him.’

She still did not understand, ‘What prognostication? You mean *SPINK-1* does not cause pancreatitis?’

‘Prognostication in medicine is an art requiring a very high level of discrimination. It is closely linked to some acts of diagnosis—such as screening for some cancers.¹⁶ Most physicians dislike and avoid making the sort of precise predictions that patients often seem to demand. Often, prognostication is not helpful, is misleading, or is even harmful to their patients.’^{17,18}

‘But I have seen many doctors give out the prognosis!’

Now I was very careful in answering. ‘Mini, we all desire as well as fear certainty in life. A desire for certainty arises, I think, in response to apparent chaos in the world.¹⁹ However, predicting about health is somewhat like predicting the weather, and relies on *fuzzy logic*.²⁰ Studies show that physicians want to be overly optimistic about prognosis by a factor of 2-fold to 5-fold, although errors at the other extreme have also been observed.^{21,22} The predictions are generally inaccurate due to deficiencies in knowledge or even lack of enough data to base predictions on.’

She wasn’t happy with this statement, ‘Then why do clinicians talk of prognosis at all?’

‘Most prognostications are contextual and are forced by patients as a step towards making some therapeutic decision.²² Many predictions are based on incomplete data, as sound data may be difficult to get. Physicians also fear that patients would hold them accountable for errors in prognostication. They invariably find the process of prognostication difficult and unsettling.¹⁷ And the above facts also do not bind a lab technician who can prognosticate with impunity without even reading medicine, and with no accountability!’

‘Yeah, you have told me as much! And I have accepted that Renee made the mistake.’

‘I am not talking of Renee. I am now talking about you. In your zeal for research, you have started thinking like a lab technician!’ I said, deliberately ignoring the ‘stop-it’ frown from my wife sitting nearby. Fortunately, Mini did not react emotionally this time and kept staring at me.

After a while she said, ‘You mean that information given by that PG was wrong?’

‘That information was given by one research worker to another colleague, trying to stress on the latter the importance of his research project. He probably would not talk the same language with his patients, but you all did.’

‘The main point is that information is accurate. Isn’t it?’

‘Such information should be discussed in a counselling session as you would do while breaking bad news.’

‘What is there to counsel? I personally asked the PG. He clearly told me that his research shows a very strong association between *N34S* mutation with pancreatitis.’

‘Strong association means nothing! Statistically, there is a strong association between driving a car and motor accidents. It only means motor accidents are more likely to occur if you are in a car. That does not mean that everyone who rides a car will have an accident. What do you know about the epidemiology of *SPINK-1* gene mutation?’

‘I knew you would come up with some interesting point. I like your example of a road traffic accident. But, I have no idea about the epidemiology of *SPINK-1* gene mutations,’ she said.

‘And you all have pronounced a death sentence on someone without even trying to find out what it means?’

‘Oh, Uncle! I didn’t. Renee did. How long are you going to blame me for her mistakes?’

‘You are the lab supervisor and doctor! How long will you keep running away from your clinical responsibilities?’

But she did not listen. She walked over to my computer and started searching on the net for ‘epidemiology of *SPINK-1* gene mutations’. She came back after 20 minutes with a radiant face.

‘Uncle, I have found the answer. *SPINK1 N34S* mutations occur in 1.3% of hospital controls, in 55% of patients with fibrocalculus pancreatic diabetes, in 20% with tropical calcific pancreatitis, and in 14% with non-insulin-dependent diabetes mellitus.²³ It still does not help Ravi because he continues to be at nearly 50 times higher risk of developing pancreatitis.’

‘Mini, the odds ratio is for finding mutation, not about developing pancreatitis. It does not mean that a person who has a “*N34S* mutation” is definitely going to develop this disease.’

She looked expectantly at me, ‘So, what would be Ravi’s risk of developing pancreatitis?’

‘I guess you can find that only by following up people with “*N34S* mutation” over a period of time to know how many of them will finally develop pancreatitis. Every genetic change does not translate into clinical disease. I am sure you have heard about incomplete penetrance and influence of environmental factors?’

She nodded.

‘Does that mean the risk for Ravi has no available estimates?’

‘Good conclusion.’

‘If nothing is known about the value of this test then why is it available commercially for people?’

‘Mini, now you are asking difficult questions.’

‘That means some people are paying to get this test done. Why?’ She sounded very perplexed.

‘Predictive genetic testing (PGT) is a relatively new science and has arisen from mapping of the human genome. This technology carries many benefits, but many risks as well. Considerable debate surrounds the moral and ethical issues regarding PGT.’

‘Yes, *SPINK-1* gene mutations would be a PGT.’ Her remark told me that she was listening.

‘PGT can be used for testing of disease carriers, prenatal diagnosis and predictive testing in a situation *where there is a family history of inheritable disease*. Each of these circumstances carries a particular set of ethical, legal or social implications, depending on the reasons why the test is being done.’²⁴

‘What implications?’

‘If I was to be diagnosed with a genetic predisposition, would I tell my brother that he too may be at risk? *What doctors tell the patient or family is crucial* because patients may make life-altering decisions based on the results of a genetic test.’²⁵

‘Just as Ravi and Renee are bent on breaking their engagement!’

‘Yes, and things get more complex when pre-implantation genetic diagnosis (PGD) tests are ordered on early-stage embryos

produced through *in vitro* fertilization (IVF). One cell is extracted from the embryo in its 8-cell stage (which does not harm the embryo) and is genetically analysed.'

'Yes, I know one will be able to choose the genes of one's child in the near future.'

'I am talking of today. Fortunately, these tests are not routinely available in our country.'

'But they are available somewhere!'

'Yes. One worry about PGD is that it may be a eugenic technology; that PGD will be used to select a child of a preferred sex, or to select a future child's aesthetic or behavioural traits, or worse, to help create a "super-race". Do want your son to be a fair-haired, green-eyed footballer?'

She wasn't perturbed. 'That is what excites me about genetics.'

'Such restrictions are inevitably intertwined with the issues of personal choice, and autonomy over one's body and one's offspring. Should it be an individual's choice or should governments make such testing mandatory?'

'I think it should be the individual's choice,' she said.

'That means it should be available to only those who can afford it? Only rich people, eh? Poor people not only should have poor health, poor treatment, but also poor genes? Is that acceptable?'

'You do have a point, Uncle!' She was now having second thoughts.

'On the other hand, if the tests are done on all, it will require individuals to learn things about themselves they may have no wish to know and potentially threaten their feeling of well-being, as in the case of Ravi.'

'You feel PGT should not be done?'

'I would not say that. It benefits many. A common example is screening of apparently healthy newborns with sickle cell anaemia. It permits the administration of prophylactic treatment that can significantly reduce infant mortality. Similarly, by screening asymptomatic infants for phenylketonuria, they can be placed on a low phenylalanine diet, which prevents mental retardation. Here, the technical accuracy of the tests is fairly certain and treatment can be administered or preventive action can be taken to avoid harm.'

'Then why were you so critical of the *SPINK-1* gene test?'

'Because no interventions are yet available to improve the outcome of these disorders, and the potential harm of this knowledge can be substantial.'

She seemed to be catching up. 'I see.'

'There are several concerns about this type of test. Some tests are imperfect predictors of future disease. After all, genes do not have the same degree of expression or penetrance.'

'I disagree with you, Uncle. These are exciting new developments and should be available to people.'

'They are available in some countries. A doctor is required to obtain an accurate family history and confirm diagnoses before testing. He is then supposed to provide information about the natural history of the disease and the purpose of the test. He also discusses the predictive value of the test, the technical accuracy of the test and the meaning of a positive or negative test. And all this is required before you proceed with testing.'

'That sounds reasonable.'

'The doctor is also expected to assess the patient's motives for undergoing the test, the potential impact of testing on relatives and the risk of passing a mutation on to children. He is supposed to discuss the potential risk of psychosocial distress to the patient and family. Apart from these concerns, such tests may result in strained family relationships, higher insurance premium and

employment discrimination. Do you have that maturity and capability?'

She suddenly changed the topic. 'You have not answered my original question. Why should a test be commercially available, which can give you a rude shock but does nothing to help an asymptomatic person? Why should anyone pay to get such bad news?'

'A lot depends on the doctor who orders such a test. Like you, many take a short cut and order it in ignorance, under peer pressure or for other reasons.'

'What other reasons?'

'Look at this newspaper report.²⁸ When the chief medical officer of a busy city hospital studied the doctors' willingness to "serve", he found that over 90% of doctors showed poor abilities to connect and empathize with suffering patients. This explains the general perception that several decisions by doctors are made for their own interest, and not for patients' benefit.²⁹ Genetic tests are no exception. If doctors and labs are benefited, the tests are likely to be asked for even if they are detrimental for patients.'

She was peering at the newspaper report I had given her, but said in disbelief. 'Are you sure?'

'Today, many parents have to dish out over Rs 30 lakh for admission of their children to a private medical college. Would they not expect their child to get that investment back as quickly as possible? Don't private hospitals in India make the patients pay for treatment of "hospital-acquired infections"?''

She looked up from the paper and said, 'Uncle, I have noted in this report that "service orientation" of doctors improves as they become old. So don't worry! Let young people be what they are. Chances are that they will all grow and finally end up like you—a preachy old person!'

NOTE: The names of characters and places are fictitious, but the concerns are real.

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