Interview

From high school dream to genomic medicine reality

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Charis Eng is the Chairman and founding Director of the Genomic Medicine Institute of the Cleveland Clinic Foundation, founding Director and attending clinical cancer geneticist of the institute's clinical component, the Center for Personalized Genetic Healthcare, and Professor and Vice Chairman of the Department of Genetics at Case Western Reserve University School of Medicine. She holds a joint appointment as Professor of Molecular Medicine at the Cleveland Clinic Lerner College of Medicine and is a full member of Cleveland Clinic's Taussig Cancer Center and of the CASE Comprehensive Cancer Center. Dr Eng was recently honored with the Sondra J and Stephen P Hardis Endowed Chair in Cancer Genomic Medicine. She continues to hold an honorary appointment at the University of Cambridge. Dr Eng's research interests may be broadly characterized as clinical cancer genetics translational research. Her work on *RET* testing in multiple endocrine neoplasia type 2 and the characterization of the widening clinical spectra of *PTEN* gene mutations have been acknowledged as the paradigm for the practice of clinical cancer genetics.

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■ You were trained in medical oncology at Harvard's Dana-Farber Cancer Institute, what led to your interest in clinical cancer genetics and genomic medicine?

Since the age of four, I had wanted to be a physician, inspired by my uncle, Professor YK Lee (Chair of Medicine in Singapore and our then Prime Minister's physician). In fourth grade in Singapore, we learned for the first time about medical discoveries – Louis Pasteur and so on. Then I wanted to be a physician and a scientist. However, at that time (and even now), there are no joint MD–PhD programs in Singapore. Serendipity sent my father to the University of Chicago and as an only child, I followed my parents to Chicago, to attend the University of Chicago Laboratory Schools. There, we had the most inspiring biology teacher, Murray Hozinsky, who loved genetics and in his spare time, taught cancer education as outreach. It was during those formative years that I decided to put cancer and genetics together. My training thereafter was chosen so that I would train myself rigorously for clinical cancer genetics and the practice of cancer genomic medicine.

■ Are there any individuals in particular you have worked with who have had an impact on the path that your career has taken?

As you can see above, in my earlier life both my uncle and Mr Hozinsky were quite important in influencing my future career. In college, I met Edward D Garber, PhD, then Professor of Genetics at the University of Chicago, when I took his introductory genetics course as a freshman. I worked in his laboratory for my honors project, and he has been my lifelong mentor for over a quarter of a century until his death in 2004. Dr Garber taught me good science (“an experiment without a control is an act of faith”), and how important collegiality and decency are in life, even working life.

I never had a mentor when I was a new faculty member at the Harvard's Dana-Farber Cancer Institute, and obviously suffered from that, but the silver lining was that those difficult 3 years taught me what mentorship is required for new faculty people, and I have always provided the very best mentorship for my own faculty members as well as to new investigators around the country and the world (the latter are usually women and/or minority investigators). I subsequently met several remarkable senior people, who provided various levels and types of mentorship. I met David Ginsburg, MD, James V Neel Professor of Medicine and Howard Hughes Medical Institute investigator at Ann Arbor, by happenstance, during a quinquennial site visit at the NIH. He has since acted as an external mentor and guide for the last 9 years. I contacted Robert J Gorlin,

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DDS, MS, the late Regents Professor of Oral Pathology and Genetics at the University of Minnesota (MN, USA), I contacted him for a collaboration and he turned out to be not only a wonderful collaborator but also an amazing mentor. Unfortunately, he passed away 2 years ago and I miss both Bob and Ed Garber very much. I almost feel that this 'old school' decency, caring and mentorship are passing as these individuals pass. I hope that I am worthy of carrying on their great tradition and work.

Obviously, in addition to mentors and individuals who have affected me positively, there were others whom I met in my academic life that also taught me what not to do. Indeed, I never wanted to be in a leadership role and was happy to be merely a triple threat. However, my early independent career was such that I decided that I needed to be in a leadership role to be able to really make a difference and help everyone: to optimally mentor junior faculty and make the correct infrastructure and environment for a happy work place. We often say in the healthcare field, 'patients first', I would rather say it is 'employees first' because happy employees make for the very best in patient care. Hence, my entering a leadership role relatively early – indeed, only after 3 years of independence. I have not looked back since.

■ You are currently the Founding Director and Attending Clinical Cancer Geneticist of the Genomic Medicine Institute's clinical component, the Center for Personalized Genetic Healthcare. Can you briefly describe the personalized healthcare programs that are being implemented in the center?

The integral collaboration between research and clinical service is reflected in the housing of both missions in one location within the Genomic Medicine Institute. The Center for Personalized Genetic Healthcare is the clinical arm of our institute and encompasses the broad practice of utilizing genetic information, in the broadest sense (e.g., from family history to genetic testing results), to provide disease risk assessment to guide clinical management, for example, organ-specific surveillance, prophylactic surgery and its timing, prophylactic

medications and behavior modification. Our practice is 100% consultative and addresses all populations, from prenatal to adult diseases, usually by teams comprising genetic counselor and physician (typically, a subspecialty trained geneticist).

■ What research projects are you currently involved with and can you briefly discuss them?

The optimal manner of achieving seamless translational cancer research is on a single platform of research, clinical care and education. On such a platform, the broad thrust of my laboratory can be characterized as clinical cancer genetics translational research, which involves the utilization of nucleic acid-based technologies to identify, characterize and understand genes that cause susceptibility to traditional and complex heritable cancer syndromes, to determine their role in sporadic carcinogenesis and to perform molecular epidemiologic analyses as they might relate to future clinical applications. Upon this framework, we are examining the genetics of two heritable cancer syndromes, Cowden syndrome, which has a high risk of breast, thyroid and endometrial cancers, and multiple endocrine neoplasia type 2 (MEN 2), characterized by medullary thyroid cancer and pheochromocytoma, and related sporadic cancers. Our work on the *RET* genotype–MEN 2 phenotype correlations is acknowledged as the paradigm for the practice of clinical cancer genetics and in fact, genetics-based personalized cancer care. Based on gene status, precise molecular diagnoses, predictive testing and type and timing of prophylactic surgery and surveillance are instituted. Currently, in an ongoing multinational study, the Eng laboratory has found that approximately 25% of population-based apparently sporadic pheochromocytoma cases are due to germline mutations in one of four genes. This has led to changing the practice of clinical cancer genetics. This multinational study now seeks to meticulously phenotype this cohort to determine if clinical clues can help target which gene to begin testing in these individuals. The genetics of susceptibility gene *PTEN*, encoding a dual specificity phosphatase on 10q23.3, is being examined in Cowden syndrome and other heritable hamartoma syndromes, as well as populations of sporadic cancers. The

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meticulous examination and documentation of clinical phenotype as well as cellular phenotype and genotype will guide referral patterns, and allow accurate gene-based cancer risk assessment, genetic counseling and clinical management.

Somatic genetics of *PTEN* and the precise diverse mechanisms of inactivation are being pursued in a range of sporadic cancers, including those of the breast, thyroid and endometrium. Gene–gene interactions and gene–environment interactions are being explored. Biochemical, cellular and functional studies are performed in the laboratory to understand the nontraditional mechanisms of somatic *PTEN* inactivation in breast cancer, including nuclear–cytoplasmic partitioning. This fundamental research is aimed at not only mechanism resolution but also hopes to identify novel targets for therapeutic and preventative drug development. Global expression analyses of one of the sporadic counterparts of a Cowden component neoplasia, follicular thyroid neoplasias, is ongoing to search for etiology and for the diagnostic differentiation of benign versus malignant follicular neoplasias. The latter will address the current challenge in fine needle aspiration biopsy diagnosis of thyroid nodules where a significant proportion are nondiagnostic.

Recent efforts in my laboratory have focused on the role of somatic genomic alterations in the tumor microenvironment in sporadic breast and prostate carcinomas and head and neck cancers. So, our work may have broad implications not only for examining the pathogenesis of common cancers but may reveal novel targets and novel compartments germane for diagnosis, prognosis, therapy and prevention.

I am particularly interested in systematically drawing out genomic and biological similarities and parallels amongst various disease processes. Thus, commonalities of processes and fundamental understanding from cancer research can be utilized and extended to other diseases.

■ A lot of your research has focused on *PTEN* mutations and their implications in human disease, how has this research helped to lead the road to personalized medicine?

As noted above, *PTEN* encodes a ubiquitous tumor suppressor phosphatase that plays key roles in the cell including cell-cycle arrest, apoptosis, genomic stability, cell motility and so on. As a result of our research, *PTEN* testing as a molecular diagnostic and predictive test are already in the clinical arena and is a model for genetics-based personalized healthcare. Finding a family-specific mutation allows for predictive testing of as yet unaffected individuals in that family with 100% accuracy, thus allowing those without mutations to be reassured that they are at population-risk for these cancers associated with *PTEN* (breast, thyroid and endometrial cancers), and those found to have mutations to undergo organ-specific (in this instance, breast, thyroid and uterus) clinical surveillance. However, while we can say having a germline *PTEN* mutation confers an up to 50% lifetime risk of female breast cancer, 10% risk of epithelial thyroid cancer and an unknown but increased risk of endometrial cancer, we still cannot pinpoint which 50%, which 10% and which x%. So at this time, everyone found to have germline *PTEN* mutations are recommended to undergo surveillance. Ongoing research in my laboratory is focusing on how to hone further gene-based personalized risk assessment and management using this as a model. We suspect that there will be gene–gene interactions and gene–environment interactions that modify phenotypic expression. Knowing that someone has germline *PTEN* mutations will also guide therapy. Neoplasias occurring in those with mutations should be responsive to mTOR inhibition (mTOR is downstream of *PTEN* and is upregulated when there is dysfunctional or absent *PTEN*) and clinical trials in this population of patients are on its way.

■ What, in your opinion, are some of the major challenges that prevent personalized genetic healthcare from being implemented?

As with anything novel, there are many challenges. Some important scientific challenges include limited knowledge and limited access to technologies. We are in what I call the ‘ugly duckling’ stage. There is accumulating content knowledge, such

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as the SNP association studies (some which are very real and validate well and many that are not), but the clinical contextual knowledge lags far behind. The technological know-how still lags, despite impressive recent advances, in easily manipulating large datasets that can ‘talk to’ one another. These two challenges will be overcome in time, but I am impatient. We must move faster for the sake of our patients and for the general public.

However, we are dependent on others who do not see, do not understand or do not want to see this vision nor the practice of personalized healthcare, inevitable as it is. Often, these individuals hold positions of authority and some may be our practicing peers. Widespread education is the answer to this, daunting as it may sound. Therefore, in order to help our institution understand and hence, be able to take advantage of genetics- and genomics-based personalized healthcare that our Center and others offer, our very insightful and foresightful CEO, Dr Delos M ‘Toby’ Cosgrove, has helped us kick off a Genetics and Genomic Medicine Education Campaign in our entire health system, which began on August 1, 2008. This is a gentle multimedia ‘learning by osmosis’ raising of genetics awareness in the entire health system (38,000 employees) and anyone and everyone who happens to walk through our health system. I believe this type of health-system-wide genetics education campaign is unprecedented in this country. I would encourage as many health systems and other venues to help educate everyone, from the public to caregivers, third-party payors to legislators, on the utility of genetics and other -omics in moving towards personalized healthcare.

Another important challenge includes reimbursement for services and the related legislative reform. I shall use the example of genetic and genomic medicine because it is at the heart of genetic- and genomic-based personalized healthcare for risk assessment of every disorder, and more recently, for choosing targeted therapies. The entire concept of personalized healthcare, especially genetic and genomic-based personalized healthcare is one major answer to curbing and indeed reversing the alarming healthcare costs in the USA. However, the greatest irony is that market forces are topsy-turvy in our field. As we emerge into

the era of genetics and omics based personalized healthcare, more and more practitioners, whether physicians or genetic counselors, are and will be required. In fact, demand far outstrips supply. Yet, reimbursement, whether salaries or otherwise, is disproportionately low in this country (it is not identical in other countries). Why? One important reason is that reimbursement codes that exist do not relate to the rather sophisticated genetics-based risk assessment and management we can do nowadays, thanks to advances in science and technology. Despite the market forces, Health Care Financing Administration rules demand that these practitioners of 21st century medicine document a whole litany of information that are not useful to genetic and genomic medicine practice (although still useful for traditional clinical subspecialties), thus draining precious time from a subspecialty in dire need of more time and more practitioners. When physician-practitioners are in short supply, practice partners such as genetic counselors are very helpful. Unfortunately, these knowledgeable practice partners are not licensed in 40 of the 50 states and although they spend hours with each patient providing genetic education, information and counseling, their services are either not reimbursable or very poorly reimbursed. Indeed, genetic and genomic medicine practitioners and genetic counselors are barely tolerated by many, but the most foresightful, healthcare institutions: at best, they are called ‘lost leaders’ and at worst, this is the first division or department to be shut down in the name of the bottom line. What can we all do about this? The best answer is legislative reform, but this may take years to decades, and will be dependent on how well we educate our legislators about the utility of personalized healthcare, both to achieve the very best patient care and as a viable long-lasting solution to skyrocketing healthcare costs. In the meantime, standardization and automation of processes and innovative time management as well as training novel practice extenders may all be helpful. Similarly, educating nongenetic physicians to co-practice with genetic counselors and genetic counselor-extenders for the most straightforward cases would also be helpful. At the Cleveland Clinic, the Genomic Medicine Institute is helping to incept some

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of these potential solutions to meet the already-growing demand for genetic- and genomics-based personalized healthcare.

■ **Where do you think personalized medicine will be in the next 5 years?** Hopefully in its golden age! Tongue-in-cheek aside, we should be humbled that the concept of personalized healthcare is not new: ABO blood typing for safer transfusions may be viewed as personalized medicine. Extrapolating from the exponential advances in the fields relating to personalized healthcare just in the last 3 years, the future appears bright. In the ideal world, everyone would have (accurate) knowledge about genetic and genomics-based personalized healthcare, such that all can take advantage of it, not only for disease management, but also to keep healthy people healthy, which will ultimately lead to graceful aging. We would have, within our clinical armamentarium, genomic and genetic tools that can diagnose and/or

predict what each person is at-risk for and to be able to select targeted interventions to effectively treat or to prevent, as the situation dictates. We would be able to understand perfectly the interaction of genes (and high-penetrance mutations with genomic variation) and genes with environment. We are currently achieving small parts of this ideal of genetics-based personalized healthcare, especially in the practice of clinical cancer genetics. I only hope that I would be alive to actually see the day of this perfection, and see the ugly duckling fly off as a beautiful swan.

Financial & competing interests disclosure

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