Interviews

The AMJ is honored to feature three interviews with distinguished leaders across the field of cancer care.

Aparna Parikh, a prominent figure at Harvard Medical School in Boston and the Director of the Global Cancer Care Program at Massachusetts General Hospital, shares her mission to improve cancer care delivery and outcomes on a global scale with us. Nancy Davidson, the Executive Vice President for Clinical Affairs at Fred Hutchinson Cancer Center in Seattle, Washington, is a renowned expert in breast cancer research and leadership. Finally, Michael Gibson, Director of Translational Research for Esophago-Gastric Cancer at Vanderbilt-Ingram Cancer Center in Nashville, Tennessee shares his aims to develop more effective treatments for esophago-gastric cancer, a challenging and often aggressive cancer type.

Aparna Parikh

Associate Professor, Harvard Medical School, Boston; Director of the Global Cancer Care Program, Massachusetts General Hospital; Director of Colorectal Medical Oncology, Massachusetts General Hospital; Medical Director Young Adult Colorectal Cancer Center, Massachusetts General Hospital, Boston, USA

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Q1 What led you to pursue a career in gastrointestinal (GI) oncology?

Once I got into fellowship, and started to see a lot of GI patients, I found a tremendous affinity towards this patient population, in terms of diversity of genders, ethnicities, and ages. I also saw a tremendous unmet need in terms of opportunities to advance science. I think, unfortunately, unlike some cancer types, survival in later stage GI cancers, and even in the early stages for some GI cancers, is still quite limited. I found that it was such a privilege to connect with patients and their families; I really appreciated, valued, and recognized the importance of those relationships during what can be just an awful time for patients. So, it was both the patient population, merged with the opportunity scientifically to hopefully make an impact on improving survival for these hard-to-treat cancers. Finally, I really enjoyed my peers. I think a lot of oncologists are special, but it takes a certain type of person to care for these complex, various sick patients, and I found an affinity for my colleagues who had gone into GI cancers.

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Q2 The incidence of early-onset colorectal cancer (EO-CRC) is rising globally. What do you believe is driving the increase of colorectal cases in patients under 50? Are there any unique challenges associated with the diagnosis and management of EO-CRC?

CRC is now the leading cause of cancer-related death amongst males aged 20–39 and 40–49. Last year, in the 20–39 group, it was the third leading cause, but now it's the leading cause. This trend is also seen in females as well. The concern is that this may surpass even breast cancer. I think a lot is still yet to be learned to really understand the underpinnings. We don't entirely know what is driving it yet. I think there is some confluence of early exposures, as early as perhaps in utero exposures; changes in weight over time, including in adolescence; the microbiome; and certain dietary and environmental exposures. This trend is happening across the world.

Our group has taken a lot of interest, not only in the research aspect to try to understand these exposures, but in investing in care for these patients, who present with unique challenges. They're young; some of them are of childbearing age; some have had children, and some are wanting children. They're in the prime time of earning opportunities and careers, both professionally to develop, but also for salary purposes, too. So, this can be a really challenging time for parenting with young kids. It's that whole spectrum of not just caring for the disease, but caring for all the other aspects of life that are directly impacted by the disease. We are actively trying to work this into our young onset program, to care for these patients holistically and comprehensively, with social worker support, guidance on fertility, and supporting the children, as a few examples. And then in parallel, our team at the Massachusetts General Hospital, Boston, USA, led by Andy Chan, along with Yin Cao from Washington University, Seattle, USA, was awarded a Cancer Grand Challenges grant, for over 25 million USD, to tackle early-onset cancers. This grant will give a particular focus to CRC, not just in the USA, but across the world. I'm leading one of the global aspects of that effort, looking at EO-CRC in India. I think it's great, because there is investment, and an urgency in really trying to figure out this very unsettling problem.

Q3 As Medical Director for the Young Adult Colorectal Cancer Center at Massachusetts General Hospital (MGH), what is your key mission, and which goals are you currently working towards?

We are getting patients in the center that are diagnosed already, so I think the overall mission eventually would be to try to figure out who is getting EO-CRC, and why, and then screen earlier. I think that a large part of the mission is on the prevention and early detection side. However, for the immediate goals of the center, it's ensuring the best care, which is always in line with trying to achieve more cures, and maintain quality of life. We offer cutting edge approaches across the spectrum of care, including bold surgical approaches, and also studies geared toward survivors. In one of the studies our program is working on currently, we are looking at coffee. There is compelling epidemiological data that coffee can be protective on the gut, have some protective impacts in the liver, and

may actually be protective in terms of colon cancer risk reduction. We're doing a prospective clinical trial, giving an incipient of coffee, and looking at outcomes that may correlate with an improvement in recurrence for cancer.

We have another clinical trial, led by one of our other faculty members, which is looking at giving a patient more comprehensive guides, as well as coaching, through the treatment of rectal cancer. Rectal cancer is much more complex than colon cancer, as it includes multimodal therapy, different side effects, and different fertility issues. So, the goal is caring for the whole aspect of the patients, and being very thoughtful around patients whose disease is metastatic: are there paths towards curing those patients? For earlier-stage patients, can we cure more, and can we prevent? And then, for patients who are undergoing treatment, can we make their whole treatment journey a little easier by providing not only the best care, but the best supportive care and survivorship care?

Q4 You are an international expert in liquid biopsies, which have emerged as a powerful tool for monitoring tumor recurrence and therapeutic responses. How do you think liquid biopsies have the potential to transform treatment approaches for patients with GI cancers?

This is such an exciting time for liquid biopsies, and I think that the liquid biopsy landscape is only going to continue to grow. I'm certain that ctDNA, and potentially other blood-based analytes, are going to ultimately transform how we're caring for patients. One of the challenges right now is that the technology is a little ahead of the therapies.

CtDNA is the most powerful prognostic biomarker we have; if ctDNA is detected after a curative intent path, the odds of that cancer coming back are incredibly high, and a better prognostic marker than many of the other prognostic markers we have. The challenge is that we don't yet have the data to know that we can do anything about that, or that earlier intervention actually matters. So, first, you need something to do. Say you have microscopic evidence of recurrence, and you don't see anything on a CT scan, it feels a little bit like a ticking time bomb, that eventually is going to manifest radiographically. But can you actually reverse that recurrence from happening? To reverse that recurrence, there are a few patients whose immune systems seem to take care of it themselves, but you may need to actually give a therapy reverse the recurrence. In many GI cancers, we have very limited therapies still. In CRC, we essentially only have one adjuvant chemotherapy, currently, that is standard of care. We offer a combination, with folinic acid, fluorouracil, and oxaliplatin (FOLFOX); 5-fluorouracil (5-FU); for recurrence prevention. And so, if you know there is recurrence, but don't have anything you can do with that, is that meaningful?

I think liquid biopsies are very empowering for patients, and it's certainly a test that I, after shared decision-making, will offer. At the moment, there's a lot of work that's happening, including some work from our group, partnering with biopharma, and working really closely with a nonprofit called Science for America. We are trying to come up with a solution for capitalizing on all the testing that is happening, to try to offer therapies for these patients. It's definitely a prognostic biomarker, but there's still not a lot we can do to reverse cancer recurrence, except for chemotherapy. And so, we're waiting for opportunities for better therapies to reverse recurrence.

Q5 MGH has been consistently recognized as one of the best hospitals in the USA. What makes MGH a leader in medical research and patient care? How can other institutions learn from the approach taken at MGH?

This may sound like a generic answer, but it's truly the reason that I came back to MGH after being away: it's the people. The physicians that come to work at MGH provide the absolute best clinical and patient care, and people pride themselves on that. I think we work collaboratively. I'd say probably the majority of places have multidisciplinary discussions and tumor boards, but at MGH, we take it a step beyond tumor boards; for our new patients, and even many of our follow-up patients, if their care requires interfacing with surgery, as well as medical oncology, we will review all the cases with the tumor board and discuss ahead of time. Then, in one visit, the patient meets the entire care team. It's very patient-centric, so the patient is not having to attend one appointment with a medical oncologist, one appointment with the radiation oncologist, and one appointment with the surgeon. A new patient is getting to meet with all their care team at one time, and we even sometimes do

follow-ups together as well. We're also tied to a general hospital, and being in a general hospital, we have the best cardiologists, infectious disease doctors, and interventional radiologists at our fingertips. Disciplines that can be very important for patients with cancer are excellent within the institution, and we have access to those disciplines. So, I think it's the collaboration, the people, and the access to a general hospital that we're embedded in, and, of course, the research mission as well.

Q6 You have a robust clinical trial portfolio, and have been actively involved in the research of novel agents for GI cancers. Are there any projects you are currently working on that you are particularly excited about?

I think in the GI cancer space, with pancreatic cancer and colon cancer, KRAS is clearly a large driver of oncogenesis, of many GI cancers and non-GI cancers as well. Historically, it has been the nut that was impossible to crack. Now that we've made some inroads with KRAS G12C, it's really exciting to see the G12D, pan-RAS, and pan KRAS space evolve. I'm running some of these RAS-based trials on the clinical side, and partnering really closely with my lab-based colleagues to understand treatment response and resistance. I think the ability to do bench-to-bedside, and then bedside-back-to-bench research, is unique.

Besides minimal residual disease, there are emerging vaccines and antibody-drug conjugates that are coming. We also remain committed to try to figure out mechanisms to make immunotherapy work. As we all know, immunotherapy in CRC has just not worked, except for the microsatellite instability (MSI)-high patients, and so, we are thinking about different strategies. One strategy that I'm excited to see shape out is built on the hypotheses that, when you have liver metastases, the liver microenvironment may be hindering the ability of immunotherapy to work. There may not necessarily be fantastic drugs to overcome that suppressive microenvironment, but can we use other modalities that we have in our toolbox, such as radiation, to eradicate the liver of disease, and get immunotherapy to work? It's still an early hypothesis, but it's the hypothesis that we have started to test and explore.

We published some data on a different dosing of radiation with immunotherapy, and we have another paper coming out soon, with radiation and immunotherapy, albeit a slightly different strategy than ablative radiation. This approach is to treat the liver with radiation, and then do bedside-to-bench work around understanding what is happening with the tumor microenvironment when you treat that. Along those lines, there's data showing that you may have activity of immunotherapy in microsatellite stable colon cancer in earlier-stage disease rather than late-stage disease; and again, maybe that's because you don't have metastases, such as liver metastases. We're working on some ideas, including with partners at Memorial Sloan Kettering Cancer Centre, on looking at immunotherapy in patients with early-stage microsatellite stable disease.

Q7 What are the most significant changes you have seen in the field of GI oncology in recent years?

The most recent changes have been the tremendous strides we've made with biomarkers. Even though immunotherapy in MSI-high disease has transformed the landscape, GI oncology is still relatively new to this field transformation. Immunotherapy in patients with metastatic MSI-high cancers, immunotherapy in early-stage patients, curing patients without any other surgical intervention, and therapies for BRAF V600E and HER2, have all only gained approvals in the last few years. KRAS G12C has not received approval yet, but is included in National Comprehensive Cancer Network (NCCN) guidelines.

What's most exciting to me is that we are starting to make headway around different biomarker-identified pockets, but we have a lot of work to still do. In the early to mid-2000s, and prior to that, there was just chemo, and then anti-VEGF and anti-EGFR therapy came to be. That was it. And then, all of these newer therapies, based on biomarker subgroups, skyrocketed. So that's really incredible to see, especially in patients who are MSI-high; we're able to cure people. But, I think it's still humbling that these biomarker subsets are small, and the majority of patients don't have biomarkers. And so, what are the therapies that we can bring into the clinic to help this majority of patients? I'm grateful to be in this space, to try to work towards figuring out what those are.

Q8 Beyond your clinical and translational research role, you are also passionate about global health. Can you tell us more about the work you do with the Global Cancer Care Program at MGH to address inequities in cancer care, in particular with the Program for Enhanced Training in Cancer (POETIC), your recent initiative to train African oncologists in their home countries?

This is an area that has been a longstanding interest of mine. I think one of the reasons I went into oncology was seeing the tremendous disparities of cancer care in low- and middle-income countries. There are a lot of disparities within the USA, and I'm not undermining those disparities, which are stark and alarming. Disparities are magnified when you are in low- and middle-income countries. We know that in these countries, the burden of disease is tremendous, and mortality, even for curable cancers, is just higher.

We've seen unparalleled progress and pace in high-income countries, and in the USA, we've seen steep declines in mortality for some cancers. We have early detection tests that cost 1,500 USD; we have immunotherapies; and cervical cancer, for example, can be prevented and cured here. However, in many low- to middle-income countries, it is a cancer that still kills people, even though we have preventive and curative approaches. Because of this, we felt that it was important as a cancer center, and as a hospital, to invest in thinking about global cancer care. We have focused along the pillars of: education, research, and clinical care. On the education end, we are trying to foster bilateral learning and partnerships, including the training program POETIC, with late trainees or early oncologists who are invested in caring for patients, and staying in Africa. We hope we are bringing people that are going to be the African leaders in cancer care and providing them exposure to how we how we care and think about patients here, and some of the newer therapies, even if accessibility is still some time away. The feedback we've had is that the relationships that can be built, and the exposures to care in different models, are quite helpful. So, that's a program that continues.

We are also starting to look at very different clinical trials, which potentially have a lot of importance and relevance to care in low- and middle-income countries, but are clinical trials that may not happen here. One such example is the idea of giving a lower dose of immunotherapy to try to bring down the cost of treatment; we know that there is some data that you don't need the doses that are currently given. If we can demonstrate prospectively that you don't need the dose that we give here, and you can get by with a lower dose with the same outcomes, it will enable cheaper access to that end, like building clinical trial capacity. But then, ensuring that downstream we actually have access to those drugs, is really important.

So, we were doing some work on capacity building for clinical trials, and partnering with colleagues that are within the Harvard ecosystem. We are also looking at other partners, such as ATOM and Harvard Law School, to see how we can help to support strategies for voluntary licensing and generics. I would say it's learning partnerships, early detection, diagnostic capacity, medicines, and clinical trials that are some of our key areas of focus. All these things keep me up at night, and I feel very lucky to be in this profession.