WORLD CANCER DAY 2021: A RETROSPECTIVE

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WORLD CANCER DAY 2021: A RETROSPECTIVE

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Cancer accounts for millions of deaths every year, and the burden of this disease is striking - testing our families, health-care systems, economies, and our scientists. In recent years, the outstanding work of researchers and vast improvements in technology has led to remarkable strides in progress. We are now able to prevent at least one third of cancers and have adapted routine-screening techniques for early detection and effective treatment. Our ability to treat and manage this shape-shifting disease has also transformed, as we have developed sophisticated therapies and adopted more tailored approaches. As a result, survival rates are reaching new highs each year, and the outlook for those affected is improving. However, there are still areas that require our attention.

Unfortunately, inequalities are well known in the field. In areas where resources are scarce and outreach is limited, cancer patients do not have access to educational programs, timely diagnosis and quality treatment. Significant knowledge-gaps also exist within cancer research, with many minority populations being underrepresented in clinical trials and underreported within the literature. Considering that scientific progress relies on the publication and dissemination of research, the lack of access to primary literature also falters, with many breakthroughs hidden behind paywalls. This not only affects clinicians and researchers, reinforcing a negative feedback-loop for researchers already struggling to obtain sufficient funding, but inhibits the next generation of curious students.

Each year, February 4th marks World Cancer Day; a movement dedicated to channeling awareness, education, and unity into collective initiatives and global action against one of medicine's toughest challenges. The theme of 2021, "I Am and I Will" was one of power, encouraging commitment and togetherness; a sentiment

resonating in today's turbulent world. In honor of this day, Frontiers in Oncology has invited a retrospective of articles from our Specialty Chief Editors, highlighting current, international challenges in their corresponding fields of oncology. Our goal is to empower continuous discussion between communities and across borders, drawing attention to the disparities faced in the field. Our achievements should be shared to maximize impact and facilitate opportunities worldwide. We know that cancer does not discriminate. So, neither should we.

We also take this opportunity to thank the wider community for their continued efforts in allowing for accelerated scientific developments, and most importantly for working with us on our mission to make science open.

Nicola Faramarzi, PhD
On behalf of the Frontiers in Oncology Editorial Office

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OPINION
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Challenges in Diversity, Equity, and Inclusion in Research and Clinical Oncology

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Disparities are common and well-known in the field of clinical oncology and cancer research. In patient care, poor access and a number of other factors disadvantage patients and this can lead to inadequate screening, prevention or treatment of cancer and poor patient outcomes. World-wide, socioeconomic status, health care expenditures and a number of other challenges contribute to disparities in cancer care and patient outcomes. Access to cancer clinical trials remains inadequate for underrepresented minorities as well as non-white racial and ethnic groups. There are also disparities and many challenges in the biomedical research enterprise that can limit innovation and that must be addressed as part of active interventions.

Keywords: diversity, inclusion, oncology, patient outcomes, clinical research, disparities

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DISPARITIES IN CANCER CARE

There is much evidence in support of disparities as an important factor in patient outcomes in the field of oncology (1–4), and this has become even more apparent in the COVID era (5, 6). Curable cancers are not screened as they should be, only to be diagnosed at an advanced stage which is more difficult to treat and which is associated with poor patient survival. The factors leading to these disparities range from lack of education and outreach to poor individuals in underserved communities, coupled with less access and lack of affordability of care (7, 8). While everyone faces the issues of increasingly more expensive healthcare and drug costs, the quality of insurance coverage including secondary coverage impacts on the care that is provided as well as the ability of poor and underserved patients to take part of it (9).

WORLD-WIDE, SOCIOECONOMIC STATUS, HEALTH CARE EXPENDITURES AND OTHER CHALLENGES CONTRIBUTE TO DISPARITIES IN CANCER CARE AND PATIENT OUTCOMES

Socioeconomic status is an important contributing factor in the quality of cancer care and disparities in patient survival. For example, in the UK which has differences in survival among patients with colorectal cancer as a function of socioeconomic status, a recent study of nearly 70,000 patients diagnosed with colon cancer between 2010-2013 identified a 21% emergency presentation rate among the affluent and a higher emergency presentation rate of 28% among the most

socioeconomically-deprived (10). The differences in emergency presentation were associated with a greater percentage of socioeconomically-deprived patients requiring emergency surgery as compared to the more affluent group (10). The authors concluded that reduced emergency presentations and the need for urgent surgery should be policy targets (10).

Health care expenditures as a function of gross domestic product can contribute to differences in patient outcomes. For example, the availability of imaging technologies, which can be a consequence of per capita health care expenditures as a percentage of gross domestic product, has been associated with favorable mortality-to-incidence ratios in kidney cancer in an analysis from 56 countries (11). In the same tumor type, there are some more expensive modern therapies such as VEGF inhibitors or immunotherapy that provide patients with advanced disease with potential for improved survival beyond surgery alone (11).

Among patients with advanced breast cancer there are a number of challenges that contribute to disparities in outcomes among underserved patient populations. Such disparities have been classified at the level of the individual or at a healthcare system level in a recent pan-European study that convened an expert panel (12). A number of challenges faced by underserved patient populations were identified including awareness, issues with communication, cultural factors, issues with data collection and clinical trial participation, issues with implementation of high-quality guidelines, and some workplace issues (12). Coordinated efforts, including cooperation between countries, to address the challenges that lead to healthcare disparities among patients with metastatic breast cancer could improve outcomes and reduce disparities among the underserved patient populations (12).

COMMUNITY OUTREACH AND IMPACT ON CANCER OUTCOMES

In the United States, NCI-designated cancer centers are committed to programs in community outreach for different racial and ethnic groups and educational programs (13). These efforts can address some barriers in communication and can facilitate altered behaviors that may impact on cancer screening and prevention efforts. It has been estimated by the American Cancer Society that 50% of cancers could be eliminated through lifestyle and behavior modifications or vaccination programs and this of course is low hanging fruit in the world of clinical oncology as cancer prevention is a much easier way to deal with cancer than having to treat advanced disease (14, 15).

DISPARITIES IN CANCER CLINICAL TRIALS

But access to care and affordability are only part of the problem with health care disparities and inequities in oncology. It is clear that currently all the major interventions in prevention and therapeutic advances occur through testing in clinical trials. Clinical trials are part of the process that ultimately allows FDA approval of drugs, devices, and population interventions such as vaccinations. It is well-documented that minority populations and often non-white ethnic groups are much less represented in clinical trials (16, 17). Although large clinical trials sponsored by the pharmaceutical industry have become global, inclusion of minorities (e.g. blacks) remains very limited. Some of the issues are related to and may be addressed by outreach but other barriers to inclusion derive from cultural and historical trust issues including "human experimentation" involving certain communities or vulnerable populations (18).

It is only with community outreach and education and work within the community that cancer centers can hope to impact on the barriers to clinical trial enrollment and inclusivity. Erosion of trust in the medical system due to historical victimization of groups or individuals in human experimentation has impacted on the willingness of racial and ethnic minorities to participate in clinical trials (19). Acknowledgments of historical mistakes is a step towards impacting on how clinical trials are conducted, and in some cases the acknowledgements may need to be personal. A good example includes tributes to Henrietta Lacks and her family for their contributions to medical science (20, 21). But there are other obstacles and challenges in the enrollment of racial and ethnic minorities in clinical trials. Such obstacles include access to care, education and communication gaps (19). Many interventions that are part of clinical trials include standard of care such as approved drugs which if not covered by insurance (or if the individuals have no insurance coverage) can add to the barriers and challenges that must be overcome to improve the inclusion of minorities and underserved racial and ethnic groups (22, 23).

LIMITATIONS IN BASIC SCIENCE WIDENS DISPARITIES

Throughout the world, the laboratory discoveries that come about from basic research are foundational as far as progress that can in the future impact on patient care. It has become clear that lack of attention to minority populations and various racial and ethnic groups has led to a knowledge gap in our understanding of cancer. The largest genomics database known as "The Cancer Genome Atlas" or TCGA has little information on minorities or different racial and ethnic groups (24, 25). It is known however that the severity of the disease can vary in different populations and that there are genetic polymorphisms that may explain the underlying differences. Cancer suppressor genes such as p53 have variants in different populations that impact on its function and its ability to suppress cancer (26, 27). Other examples include cancer susceptibility genes such as BRCA1 and BRCA2 that occur more commonly in Ashkenazi Jewish populations (28).

In recent years there has been growing emphasis on scientific studies on biological variables such as gender and minorities including racial and ethnic groups (29, 30). While there is some improvement in clinical trial enrollment, there remains a major gap and much progress to be made. Attention to these issues will improve our ability to understand cancer biology in different contexts from the biological behavior of cancer in different groups to the metabolism and toxicity of drugs in different hosts to the efficacy of the therapeutics. Indeed, there is a need to

address diversity and equity if we are to fulfill the promise of precision medicine to provide the best care possible to each individual (31–33).

DISPARITIES IN ACCESS TO THE PUBLISHED LITERATURE

As basic scientists and clinicians undertake efforts to perform basic and clinical research or clinical care in oncology there is a world-wide challenge often faced with lack of access to primary literature (34). This includes historic papers in major journals that remain behind a paywall inaccessible to anyone. This may even include manuscripts investigators authored themselves and paid to publish but cannot access as their own publications. This situation extends to students, and members of the public whose taxes often supported the research. It also extends to populations of other countries where access to the literature is limited or restricted. In the old world of a few decades ago, individuals would go to the library and access the literature for free. In today's online world this is no longer possible in many cases. Efforts have been mobilized to ensure that NIH funded research is accessible, however often with delays of a year or more. While some journals are allowing immediate open access for a fee to authors, the problem still remains with large amounts of inaccessible especially older literature that should be freely available.

LACK OF DATA SHARING LIMITS PROGRESS IN THE FIELD OF CANCER RESEARCH

The creative process that leads to scientific discoveries and therapeutic advances to help reduce the burden of cancer needs all the help it can get. Information flow and data sharing are high priority areas for improvement. One of the great contributions of the Biden Cancer Moonshot in the United States was a recognition that breaking down silos and allowing free exchange of knowledge could accelerate life-saving discoveries (35, 36). Access to data is like access to the literature. Having more experts look at problems from different points of view is a key to advancing knowledge. This is also true in research laboratories where the greater the diversity of members the higher the chance that certain breakthroughs may be achieved.

INEQUITIES IN BIOMEDICAL RESEARCH

While we address the inequities described, in our opinion, we need to pay attention to the viability of the biomedical research enterprise. There are huge inequalities from the elite well-funded laboratories at elite institutions, the enormous endowments and prestigious foundations that support them, to the "soldiers" in the field trying to do research against all odds with NIH grant pay-lines in single digits. These inequalities have in the last two decades created a culture of "haves" and "have-nots" with widening gaps as technologies advance and institutions build up their research infrastructure. These realities of how research is conducted in the US, in terms of available resources, are threatening the future of biomedical research as a career in research may no longer be appealing to the brightest students.

There is a grave danger, in our opinion, in the lack of support for science and for the investigators who pursue it. These very investigators have had to deal with ever increasing regulatory burdens in laboratory, animal research or human subjects research as well and the burdens of grant writing that are seemingly never ending. It really doesn't make sense nor is it acceptable in any profession for researchers who are hired as faculty based on their outstanding accomplishments to be for the rest of their career trying to secure significant portions of their salaries on very competitive grants.

The situation is even more challenging for those who also practice medicine and have to deal with some of the very challenges mentioned earlier such as communication with insurance companies to approve needed care for patients. There is also the ever-increasing burden of clinical documentation with electronic health records that hinder the physician-patient relationship, rather than helping it.

Efforts to enhance diversity and inclusion in the work-force need to consider these types of challenges that are faced and which get in the way of needed progress. Solutions must address not only these issues but obstacles faced by young families and women faculty who often juggle their academic careers with child care and care of family members such as elderly parents. Solutions at our great institutions must include having role models and mentors and an environment that is cognizant of the challenges and is actively working to deal with them. For example Cancer Research UK (CRUK) has various support networks (https://www.cancerresearchuk.org/about-us/charity-jobs/working-with-us/equality-diversity-and-inclusion) and flexible mechanisms to support research activities (https://www.cancerresearchuk.org/funding-for-researchers/applying-for-funding/policies-that-affect-your-grant/flexible-research-careers-funding-policies?_gl=1*7mecl7*_gaMTIwNDE3MTQ5Ny4xNjE0ODE3NDI*_ga_58736Z2GNN*MTYxNDgxNzQyMC4xLjEuMTYxNDgxNzcyNS4yNQ.&_ga=2.168422753.1163472191.1614817421-1204171497.1614817421). Efforts have begun to educate faculty at most US medical schools about conscious and unconscious biases that have relevance to everything that goes on in academia, and which present barriers and widen the gaps in disparities. Early efforts through the NIH are beginning to address some of these issues to facilitate greater minority recruitment of biomedical faculty at US Universities (https://www.nih.gov/news-events/news-releases/nih-fund-cohort-recruitment-development-program-enhance-diversity-inclusion-among-biomedical-faculty).

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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PERSPECTIVE
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Challenges and Initiatives in Diversity, Equity and Inclusion in Cancer Molecular Imaging

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A diverse biomedical workforce is essential to achieve excellence in patient care, clinical translational, and basic research. Diversity, equity, and inclusion challenges in cancer molecular represent a combination of the challenges facing the science, technology, engineering, and mathematics (STEM) field, and challenges in Radiology and Nuclear Medicine. Although there is a growing awareness of conscious and unconscious bias that negatively affect the cancer imaging world, many challenges remain such as overcoming barriers to entry into the pipeline, avoiding program dropout, and providing long-term career prospect. The COVID-19 pandemic has resulted in a significant setback and further highlighted problems faced by women and underrepresented minorities. In this perspective, we have identified some of the challenges faced and highlighted ongoing and future initiatives to address these challenges.

Keywords: diversity & inclusion, cancer molecular imaging, equity, radiology, STEM - science technology engineering mathematics

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INTRODUCTION

Diversity of our population in terms of geographic and economic backgrounds, skin color, age, gender, sex and sexuality is a major hallmark of our century. Currently, racial and ethnic minorities make up nearly 40% of the United States population. By 2050, non-white people will represent more than 50% of the general population (www.census.gov). As a consequence, building a diverse biomedical workforce is essential to excellence in patient care, clinical translational, and basic research (1, 2). Diverse teams are better at solving complex problems and relate better to the general public. Diversity has been linked to improved access and quality of care for minorities and female patients (3, 4). Female and Underrepresented in Medicine (URiM) faculty serve as important resources for patients from diverse backgrounds and important role models and mentors to minority trainees (5).

The cancer molecular imaging field represents a fusion of expertise in various disciplines such as molecular biology, engineering, chemistry and computational sciences. Because molecular imaging is increasingly being integrated into diagnostic imaging and imaging directed treatments and interventions, clinical radiologists and nuclear medicine physicians form an integral part of the field. The challenges for diversity, equity and inclusion in this field therefore represent a combination of the challenges facing the science, technology, engineering and mathematics (STEM) field, and challenges in Radiology and Nuclear Medicine.

The past decade has clearly witnessed a growing awareness of conscious and unconscious bias that negatively affect the entire Radiology workforce. Among training programs of 20 sub-disciplines in clinical medicine, diagnostic radiology ranks 17th in female and 20th in underrepresented minorities (URM) representation (https://doi.org/10.1148/radiol.13130101). Thus, there is an urgent need for Radiology to address its dire underrepresentation of female and racial/ethnic representation in both preclinical molecular imaging research and clinical-translational molecular imaging. Overcoming barriers to entry into the pipeline, avoiding program dropout and providing long-term career prospects are all important challenges towards the goal of successful careers of those who are underrepresented in the field. The COVID-19 pandemic has presented additional barriers and fractures in our work-force, and further highlighted problems faced by women and URM. While the switch to virtual academic interactions, remote teaching and training, and virtual radiology, has allowed more flexibility, overall the disruption to childcare and school routines has significantly negatively impacted women and URM. As discussed in a recent study (6), URM researchers across the board from students and trainees to faculty have faced multiple challenges due to the pandemic due to wide-ranging issues such as a disparate loss of opportunities for students and trainees, and the smaller research programs of URM researchers making them vulnerable with the shutdown of research operations.

CHALLENGES IN DIVERSITY, EQUITY AND INCLUSION

The importance of diversity in STEM to increase talent and problem solving, and to improve long-term economic growth and global competitiveness, is clearly recognized (7). While significant inroads have been made in actively supporting diversity and inclusion in the STEM field, published numbers indicate that a disproportionately low number of women and black, Latinx and Native Americans enter the STEM fields, and specifically, Radiology. Some of the barriers include socio-economic disparities that can lead to inability to pay for colleges, reduced access to advancement placement courses, and challenges arising from associating with different demographics and cultural majorities (A Guide for Minorities in STEM: Increasing Workplace Diversity, 2020). In academic and research centers, while discrepancies in the numbers of women and URM graduate students, fellows and junior faculty is decreasing, women and URM numbers significantly dwindle in the transition to senior faculty and leadership positions. The importance of role models and mentors that demonstrate diversity in leadership roles can contribute significantly to reducing disenfranchisement of women and URM in STEM.

Diversity of trainees and faculty in the field of Clinical Cancer Molecular Imaging is important because cross-cultural communication and access to a diverse group of physicians leads to better health outcomes (8). Cultural competence is the ability to understand and effectively communicate with people from different cultures (9). Healthcare providers with broad language competence (10–13) and an understanding of culture-specific concepts (14–16), positively impact medical care by creating closed-loop communications, reducing medical errors and enhancing positive health outcomes.

However, despite significant efforts of academic institutions, the representation of female and racial/ethnic minority faculty members in Academic Radiology departments remains low, especially in higher ranks and leadership roles. Cater et al. reported that female radiologists comprise 33.5% of all radiologists worldwide, with the lowest proportion in the United States (27.2%) (17). The problem starts with our pipeline: West et al. reported that all radiology fellowship programs in the U.S. suffer from variable levels of gender and ethnic disparities (3). Reported relative numbers of female faculty were 15.4% in interventional radiology (18), 23% in neuroradiology (19), and 30.66% in musculoskeletal radiology (20). Of particular concern is the decreasing relative number of females compared to males within higher academic ranks and in radiology leadership positions (19, 20). For example, a study by Ahmadi et al. reported that 87.5% of neuroradiology leadership positions were occupied by men compared to 12.5% occupied by women (19). Even in breast imaging, where female faculty predominate, no correlation was noted between female gender and leadership positions ($p = 0.57$) (20). Black and non-white Hispanic faculty represent less than 10% of Radiology faculty nationwide, with reported proportions in the order of 2% Black and 6.2% Hispanic faculty (18).

Underrepresented minorities in Radiology, especially black and hispanic people, are used to being the "only" in their cohort, program, or department. Black and hispanic people remain starkly underrepresented in almost all STEM graduate programs, and this is only exacerbated as we consider postdoctoral fellows, faculty, and leadership roles. In addition to the general challenges that face all trainees in the fast-paced and often competitive environment of academia, this lack of representation and visibility can often leave URM students and other marginalized groups feeling like this space is not meant for them. Unilateral hierarchies represent the root cause for many acts of microaggression and disparities reported by racial/ethnic URM in STEM fields. Therefore, increasing the quota/proportion of underrepresented minorities alone is not enough. We need to increase the representation of qualified underrepresented minorities in leadership roles in order to ensure that every team member has an advocate at the leadership table, when decisions are being made. Introducing powerful advocates for everyone will reduce the risk of discrimination and harassment at the workplace and provide our students and junior faculty with a diverse set of role models.

INITIATIVES IN CANCER MOLECULAR IMAGING

The infrastructure to meet these challenges should combine top-down and grass roots approaches to increasing diversity and inclusion in the STEM and cancer molecular imaging fields. Programs that identify talented candidates early on, and

continue to support them throughout their careers, would increase the success of women and URM, and build a cadre of leaders that would serve as role models for future generations. Financial support for such programs through philanthropy or other funding mechanisms is critically important.

Department leaders, scientific societies, and programs are recognizing the importance considering and including qualified women and underrepresented minorities in leadership training programs, committees, and consideration for awards and honors. The American College of Radiology (ACR) has established a Commission for Women and Diversity with the intent to celebrate diversity and actively promote inclusion at all levels of training, practice and leadership. The Society of Nuclear Medicine and Molecular Imaging (SNMMI) has established a Diversity, Equity and Inclusion Task Force with the goal to develop strategies to make all people feel that they belong to and can bring their true authentic self to their work place. These efforts are important, but should be expanded. Opportunities should be aggressively advertised to women and underrepresented minorities through appropriate venues, as in some instances, there may be an absence of awareness of these opportunities. There should be expanded training to raise awareness of conscious and unconscious bias. Biases, when these are identified, should be directly confronted and addressed (21). At the same time, evaluation biases need to be minimized by maximizing blinded reviews of research articles, grants and job applications. Dedicated courses and workshops focused on the importance of diversity and inclusion, and on identifying and eliminating conscious and unconscious bias are important to break down barriers to diversity and increase inclusion. The initiatives can be tailored to meet the needs of the situation. For instance, the stressors from the COVD-19 pandemic, in addition to the ongoing disparities regarding women and URM trainees, students, and faculty, have highlighted the urgent need for academic centers to implement corrective actions for all researchers and especially for women and URM. An excellent overview of strategies for pandemic-related researcher needs presented by Carr et al. (6) can also be adopted and implemented as general strategies to advance Diversity and Inclusion in academic centers. Creating internal bridge funding strategies, and developing guidelines for unbiased distribution of seed funds, may ameliorate, to some extent, the major set-back of the pipe-line and career advancement of URM and women that has occurred due to the pandemic.

Trainees

Training in clinical molecular imaging provides a broad foundation for a wide range of career opportunities, ranging from Radiology faculty positions, research and management positions, radiation physicist positions and careers in computer sciences at Universities and the industry. Thus, our field is uniquely poised to impact diversity in STEM through pipeline programs. While graduate students and postdoctoral fellowship candidates can apply to a variety of training programs, none of these programs specifically address challenges and disparities experienced by trainees from URM backgrounds. Many R1 Universities receive more than 500 applications every year for less than 10 training spots provided by existing training programs. While the selection committees for these programs carefully review every application and consider trainees from all backgrounds, it is impossible to move the needle in terms of URM representation through these programs alone. The marked underrepresentation of Black and Hispanic students specifically would require influx of these students into the academic system at a higher rate. Adding training spots to existing training programs, perhaps through philanthropic initiatives, could impact the current underrepresentation of URM students in the field of molecular imaging more effectively by enabling an increased influx of URM trainees into our discipline. This increased number of URM trainees would lead to an increased availability of qualified candidates for faculty positions, and ultimately, increased representation of URM among Radiology faculty.

The imposter syndrome is experienced by high-achieving individuals who doubt their achievements. In a recent study conducted by our team at Stanford (22), we found that female and racial/ethnic minority status was strongly associated with self-reported imposter syndrome (p=0.006). By contrast, white male status was strongly associated with perceived recognition of their efforts (p=0.002). An imposter syndrome might prevent URM and female trainees to submit their scientific manuscripts to high impact journals, to apply for faculty positions at R1 Universities and to apply for leadership roles at different stages in their career. Dedicated mentoring, sponsorship and public acknowledgment of accomplishments can significantly improve the confidence of these individuals to try new responsibilities.

Junior Faculty

Despite substantial monetary investments in gender and racial/ethnic equality programs, large proportions of minority faculty members drop out at the early and mid-career stage (23). Daily microaggressions can significantly impact the experience and long-term career success of underrepresented minority faculty. Examples include inappropriate comments or minority team members being relegated to mundane tasks. Intentional and unintentional prejudices can lead to biased formal evaluations of minority faculty. A highly effective approach to unbiased faculty evaluations would be to replace subjective evaluations by objective and measurable evaluation criteria, such as number of publications, impact factors and grants rather than "popularity scores", which nurture and favor office politics over productivity. As mentioned earlier, evaluation biases should be directly addressed by implementing blinded reviews of research articles, and grant and job applications.

Many initiatives provide dedicated funding to support research efforts of junior faculty *via* reduced paylines or dedicated funding opportunities that are restricted to faculty at junior ranks. While specific support for junior faculty is certainly appreciated, many junior faculty find themselves stranded at the mid-career level, when these funding sources are not available to them anymore. This often leads to a dropout of highly qualified personnel after 6- or 7-figure investments by their institutions

and/or tax payers. It is an unspoken reality that many academic faculty nationwide spend the vast majority of their time writing grants. This cannot be in the interest of medical innovation and discovery. As a community, we have to address this problem: We have to expose research-interested academic radiologists to a range of career options at an early career stage so that the field can leverage their skills rather than seed-funding blind ending careers. For clinical molecular imaging researchers with an interest in clinical-translational research, more long-term funding opportunities should be provided such that researchers can truly focus on research and discovery, without constant distractions by grant-writing duties and fears about their short or long-term job security. While this applies to all researchers, long-term career security is especially important for researchers from financially underserved communities. Members of financially affluent backgrounds may be more open to taking risks with regards to long-term financial insecurity. On the other hand, members from financially disadvantaged communities may put a higher emphasis on financial security, thereby excluding academic research jobs as viable career options.

Established Investigators

Providing adequate resources and time for both clinical and research work is essential to maximize the value and excellence of clinical cancer molecular imaging. Our data at Stanford showed, in accordance with others, that female and racial/ethnic minority faculty reported less access to resources compared to male faculty (22). For example, several female faculty noted that significantly more intra-mural grants were assigned to male compared to female faculty. The vast majority of named professorships in Radiology and Molecular Imaging nationwide are assigned to men. This disparity has implications on productivity and leadership development. A study by McDonald et al. of faculty publication records at 4 large academic radiology centers found that male faculty had a significantly higher percentage of last author publications than female faculty ($P < .0001$), while female faculty had a significantly higher percentage of first author publications ($P = .0025$) (24). The first author is typically conducting the "hands on" experiments, while the last or senior author is often the division/group leader. It has been described that women are disproportionally doing the front-line work and "institutional housekeeping" while men disproportionally build their academic record as resource owners (25). It would be interesting to evaluate, if resource allocation precedes academic productivity or *vice versa*. In other words: Does promotion to a leadership role lead to increased productivity as a result of increased access to resources, which in turn is rewarded with further promotions. The composite of individual psychological experience of bias and lack of clearly defined promotion metrics, combined with lack of individualized support and guidance feeds this overall issue. Initiatives at a nationwide level should explore the efficacy of interventions that help to mitigate this problem. Likely individualized sponsorship would help greatly.

CONCLUSION

An inclusive world with scientists and clinicians that represent all spectrums of our society is one of the most worthwhile and important goals of our century. The COVID-19 pandemic has clearly posed additional challenges in attaining this goal. These challenges have served to highlight the importance of global co-operation and inclusion, and our resilience as we work towards a better world. Academic and research institutions, medical and academic societies, medical practices have all had to adjust to the disruptive forces of the pandemic to bridge distances using virtual interactions for outreach, teaching and training. These virtual capabilities and tools can be exploited in molecular imaging to break down barriers to inclusion, and to access high level specialized education, so that opportunities can become equal for everyone, and for the field of clinical and research molecular imaging to benefit from a diverse, vibrant, global community.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors have equally contributed to this perspective. All authors contributed to the article and approved the submitted version.

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OPINION
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Current Challenges in Hematology: Awareness, Prevention, Equity

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INTRODUCTION

Hematologic malignancies make up approximately 10% of all cancer types in the USA, and the management of patients suffering from hematologic malignancies has dramatically changed over the last 20 years (1). Death rates have reduced across the various malignancy types, and rapidly fatal diseases, such as chronic myeloid leukemia, have become curable thanks to therapies like Imatinib Mesylate, occasionally termed an oral 'magic bullet' (1–3). Pathologies ignored by most, with little or no therapeutic possibilities, based only on conventional chemotherapy, have captured the spotlight: chronic lymphocytic leukemia, C(LL)inderella, very recently became a star, with numerous ongoing clinical trials and several novel agents approved (4, 5). Another case in point is the outcome of multiple myeloma (MM), the second most frequent hematologic malignancy type after non-Hodgkin lymphoma (NHL), has significantly improved in recent years, again thanks to the introduction of novel therapeutic agents (6). A better understanding of disease heterogeneity, together with the discovery of novel targeted agents to be used in combination with chemotherapy, has also significantly improved the prognosis of acute myeloid leukemia (AML), the big bad wolf for any hematologist (7). Lastly, the advent of Chimeric Antigen Receptor T (CAR-T) Cells has brought upon similar advances and positive outcomes in a number of patients, and as of February 2021, there are four CAR-T Cell therapies approved by the FDA for use in patients, and numerous additional ongoing clinical trials. CAR-T Cells are a novel personalized cancer therapy which acts directly on the immune system of patients, making it able to recognize and destroy tumor cells, and has granted the opportunity to treat advanced forms of hematological malignancies in resistant and relapsed patients, and to survive (8, 9).

What challenges does a hematologist face in 2021, if any? As a matter of fact, all that glitters is not gold. This year's World Cancer Day is focused on awareness, prevention and equity. When thinking about it, it is not strange that these are the themes that were selected this year. Let's explore why.

AWARENESS

Wikipedia defines awareness as "the state of being conscious of something. More specifically, is the ability to directly know and perceive, to feel, or to be cognizant of events" (10). When applied to patients, awareness is the state of being conscious of the disease and its symptoms. It is therefore necessary to ensure that screening, early detection, and education surrounding the disease is further increased. A lack of awareness can be attributed to a number of reasons. An inability to access

information, and more importantly accurate information, is one key reason for a lack of awareness. This, unfortunately, can often be made harder through the presence of stigma associated to cancer, which can prevent individuals from taking preventative action, or even receiving medical check-ups, out of fear. A case in point is, according to an UICC report, only 36% of people surveyed across Africa view cancer as a major health issue, and 25% believe that cancer has no cure (11). If people are aware of a disease and its symptoms, they are more likely to act in order to prevent it from happening to them, through means such as participating in screening programs, regularly checking their health status, and visiting their doctor when they experience symptoms. As a result of this aforementioned lack of awareness, people may come to hospitals when their disease has degenerated, or reached an advanced stage, resulting in lower possibilities of receiving effective treatment and curing their tumors. A case in point is in Indonesia, where approximately 70% of cancer patients visit a physician once their cancer is at a late stage, thus reducing their overall chance of survival (11).

Lack of awareness may not only worsen clinical outcome, but it can also be divisive in society and affect quality of life. As a hypothetical example, a young child with leukemia (in remission) may not be invited to attend a peer's birthday party as the hosts are scared to invite a leukemic patient, stemming from the stigma associated to condition, immunodeficiency, risk of bleeding, and in some cases, there can even be a misconception that the cancer itself is contagious.

Why is there a push to increase awareness surrounding leukemia, lymphoma, myeloma, and other hematological malignancies? The best opportunity for awareness campaigns is in changing attitudes and behaviors toward cancer prevention, screening, and early detection. Unfortunately, these strategies are very limited in leukemia, lymphoma, and myeloma, given the rapid and aggressive course of these diseases. However, awareness and education can initiate a cascade. Increased awareness and education lead to further support, which in turn allows for more research. And research leads to new and better treatments. With this aim, September was selected to be Blood Cancer Awareness Month each year, in order to raise funds for research and patient support organizations involved in hematological malignancies.

Unsurprisingly, a Google web search of 'cancer awareness month' is dominated by results related to "Pink October", which pertains to breast cancer awareness. Breast Cancer Awareness month, famously associated with the color pink, receives huge amounts of publicity, with numerous articles being published in popular media outlets rather than scientific journals. A PubMed search on 'cancer awareness months' identifies even fewer publications, and once again the results are predominantly related by breast cancer. Jacobsen and Jacobsen (12) investigated a potential relationship between the Breast Cancer Awareness Month initiative, and the number of subsequent breast cancer diagnoses in the following month, November, looking at years prior to, and following the introduction of the initiative (using SEER data to investigate such numbers). The authors demonstrated that between 1973 and 2005 there were some evident "spikes" in diagnoses in the month following Breast Cancer Awareness month, November (12). Two of these apparent increases in diagnoses could in fact be attributed to an overall increased awareness related to breast cancer diagnoses in females, as opposed to, for an example, and advance in diagnostic methods. In particular, there was a clear spike in November diagnoses in the mid-1990s, in the 3 years following the initial introduction of Breast Cancer Awareness Month. However, this increased trend did not continue in subsequent years (12). Breast cancer screening rates have significantly increased in the last 30 years, and the distribution of breast cancer diagnoses throughout the year has become more consistent and uniform, without any additional "November spikes". In brief, the introduction of a dedicated awareness month initiative was initially highly effective, and it is plausible that the importance of mammography was recognized thanks to the effect of a short-term awareness campaign, bringing further attention to breast cancer.

Awareness is extremely important also for patients who have endured and survived cancer, in particular the pediatric population, who are exposed to late effects of treatment. Such effects can have varied onset – months or even years after treatment, and are heterogenous in nature spanning from physical, cognitive, or psychological. A recent systematic literature review, with input from >20 different organizations, resulted in the creation of LEAP^3 AHEAD (Late Effects Awareness for Patients, Physicians and the Public; Advancing Health and Eliminating All Disparities), a multi-dimensional website centered on late effects (13). This is the first interactive, international website dedicated to acute lymphoblastic leukemia childhood cancer survivors and families, as well as physicians. It was developed with the aim to increase awareness about risks, detection, diagnosis, treatment, and prevention of medical and psychological late effects (13). Awareness and prevention are two sides of the same coin.

PREVENTION

Wikipedia defines prevention, referring to healthcare, as "preventive healthcare": measures to prevent diseases or injuries rather than curing them or treating their symptoms (14). Although great strides have been made to cure several types of cancer, cancer remains the second leading cause of death worldwide. Instead of waiting for state-of-the-art treatment breakthroughs, individuals can take action to protect themselves. Examples of such actions include participating in early screening, as well as following some general recommendations and tips to prevent cancer development. Such recommendations often form the basis of national initiatives aimed at curbing cancer rates. Early diagnosis is important; however, reducing the risk of getting cancer is even more important. Avoiding tobacco in all its forms, consuming a balanced diet, actively avoiding obesity, exercising regularly, consuming alcohol with moderation, and making quality sleep

a priority, are easy and apparent ways to help prevent cancer, even if many people do not strictly follow them. Getting vaccinated, protecting our body from the sun, avoiding risky behavior such as unnecessary exposure to radiation or to industrial and environmental toxins are important things to keep in mind, especially in preventing hematologic neoplasms.

In order to stress the importance of our behavior in preventing cancer development, we appoint several examples. 1. The bone marrow is one of the most radiosensitive organs, and there is clear evidence that the risk of developing AML, acute lymphoblastic leukemia (ALL), and myelodysplastic syndromes (MDS) are higher after exposure to moderate-to-high doses (>0.5 Sv) of ionizing radiation (15). Moreover, exceptionally high relative risks of deferred leukemia have been described following radiation exposure in childhood (15, 16). The majority of exposures, however, are typically at low doses as they result from natural background radiation, diagnostic medical tests, or occupational exposure. Accordingly, evaluating risks in the low dose range is critical for radiation-protection purposes, especially in children. Interestingly, recent data suggest that even exposure to low-dose radiation <100 mSv, or even <50Sv during childhood, may be associated with increased risk of childhood ALL and subsequent MDS/AML (15, 16). This finding is particularly relevant as computerized tomography is a common source of low dose radiation. *Nikkilä et al.* demonstrated that cumulative red bone marrow dose from computed tomography (CT) scans showed an excess odds ratio of 0.13 (95% confidence interval: 0.02 - 0.26) per mGy. In other words, whilst CT may be a helpful diagnostic tool, it is on the other hand a source of low-dose radiation which can subsequently result in an increased risk of leukemia. 2. There is abundant evidence about the association between viral infection and lymphoma development. Epstein-Barr Virus infection is responsible for African Burkitt lymphoma, and increases the risk of both Hodgkin disease and follicular lymphoma (17, 18). Furthermore, Hepatitis B and C infections are similarly associated with an increased risk of non-Hodgkin lymphoma (19), with an additional risk increase in patients with concomitant HIV infection (20). *Fabula docet:* prevention is (at least) half of the cure, and the higher is the awareness, the better the prevention.

EQUITY

Equity can be a difficult concept to comprehend as the term itself has multiple definitions depending on the context, ranging from a financial setting, to in this case, the public health setting. Health equity, in its simplest form, means giving patients the care they need when they need it. The US Institute of Medicine indicates, health equity is "providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status" (21). Accordingly, and before looking at health equity in cancer, it is quite clear that awareness, prevention, and equity all go hand in hand. Higher rates of chronic and expensive illnesses, together with high rates of uninsured people among lower socioeconomic and minority populations, result in a greater reliance on emergency services, higher treatment costs, and, finally, a financial strain on providers and government programs. As an example, in rural parts of the USA, employer insurance coverage is lower than in comparable urban areas (22). Similarly, lower socioeconomic status among cancer patients has been seen in some cases to be associated with an elevated risk of suicide (23). We know that preventive medicine and early interventions are proven means to saving money and lives.

Returning back to cancer, the gains that have been made in the reduction of cancer incidence and mortality are unfortunately not shared by everyone. Disparities still exist with regards to ethnicity, gender, race, socioeconomic status, and geography (24). As an example, a review of global access to cancer medicines in 2020 showed a marked difference in the availability of cancer medicines between countries of varying income levels. Only 10% of countries around the world listed all 25 cancer medications that appear on the World Health Organizations Model *Lists of Essential Medicines*. In contrast, on average, only 9 listed medicines were available in low-income nations (25).

In 2008, the National Institutes of Health Centers for Population Health and Health Disparities published a framework to elucidate the ecological determinants of disparities in cancer incidence, morbidity, and mortality (26). Interventions to eliminate disparities may be aimed at the multilevel factors, required to achieve improved cancer outcomes. Health systems are paying attention to disparities in the quality of their care and seeking remedies as healthcare costs rise, and consumers demand action.

In conclusion, awareness, prevention, and equity are still hot topics, even in 2021, as people still die of cancer in 2021, still due to a lack of awareness, prevention, equity. This is why it is so important that the 2021 World Cancer Day is dedicated to awareness, prevention and equity

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the writing of this manuscript.

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PERSPECTIVE
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World Cancer Day 2021 - Perspectives in Pediatric and Adult Neuro-Oncology

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Significant advances in our understanding of the molecular genetics of pediatric and adult brain tumors and the resulting rapid expansion of clinical molecular neuropathology have led to improvements in diagnostic accuracy and identified new targets for therapy. Moreover, there have been major improvements in all facets of clinical care, including imaging, surgery, radiation and supportive care. In selected cohorts of patients, targeted and immunotherapies have resulted in improved patient outcomes. Furthermore, adaptations to clinical trial design have facilitated our study of new agents and other therapeutic innovations. However, considerable work remains to be done towards extending survival for all patients with primary brain tumors, especially children and adults with diffuse midline gliomas harboring Histone H3 K27 mutations and adults with isocitrate dehydrogenase (IDH) wild-type, O^6 guanine DNA-methyltransferase gene (*MGMT*) promoter unmethylated high grade gliomas. In addition to improvements in therapy and care, access to the advances in technology, such as particle radiation or biologic therapy, neuroimaging and molecular diagnostics in both developing and developed countries is needed to improve the outcome of patients with brain tumors.

Keywords: neuro-oncology, neurosurgical oncology, oncology, neurology, pediatrics

INTRODUCTION

If one could infer by attendance at major neuro-oncology conferences and the representation of pediatric and adult neuro-oncology at international oncology meetings, there has been an influx of new investigators, interest and significant advances in biomedical research pertaining to improving diagnosis, risk stratification, and treatment for children and adults with primary brain tumors. However, research progress has not yet had the anticipated impact on patient outcomes despite the promise. In the following article, we discuss several topics of current interest to the neuro-oncology community to reflect the directions the field is taking.

DIAGNOSTIC AND PROGNOSTIC CONSIDERATIONS

The 2016 update to the World Health Organization (WHO) Classification of Tumours of the Central Nervous System brought important refinements, including but not limited to molecular genetic subgroups of medulloblastoma and the introduction of diffuse midline glioma with Histone H3 K27 mutations (1). With the advent and subsequent implementation of platforms such as whole genome sequencing (2), single cell nucleic acid sequencing (3–7), nanostring technology (8, 9) and DNA methylation (10–12) profiling, some diagnostic categories have been replaced, such as the former primitive neuroepithelial tumor (PNET)grouping (13), whereas more common tumors such as low grade gliomas and glioblastoma (GBM) in pediatric and adult age groups are being split into subgroups specified by molecular and genetic considerations (14–20). The Glioma Longitudinal Analysis Consortium (**GLASS**) was established to assess genomic, epigenomic and other molecular changes such as tumor mutational burden and mutational signatures that occur over time from initial diagnosis to tumor progression/recurrence, including in response to chemotherapy and radiation (19, 21). Although driver mutations were retained at recurrence, prior therapies such as alkylating agents contributed to acquired mutations, including a hypermutator phenotype. Furthermore, selection of subclones with disease progression portended a worse prognosis (19). Other consortia, including the Consortium to Inform Molecular and Practical Approaches to CNS tumor Taxonomy (**cIMPACT-NOW**) (22, 23) have been organized to make further refinements that will be incorporated into the next edition of the WHO Classification.

Going forward, the task will be to prospectively study these subgroups in well designed clinical trials limited by smaller numbers of patients with these specific diagnoses. Significant pre-clinical and basic research is needed to identify actionable therapeutic targets within these subgroups. Furthermore, once appropriate therapies are identified, successful clinical trial accrual will likely require international collaboration given the limited patient numbers. However, many of these advanced molecular diagnostic technologies are not accessible in the developing world limiting the ability to both include these regions in trials and appropriately apply new treatments to the patients living there. Efforts to democratize molecular pathology using more widely available assays may be necessary, even at the cost of precision.

Other important advances include **liquid biopsy** for both initial diagnosis and at the time of progression/recurrence, such as for diffuse midline gliomas and to follow responses to therapy (24, 25). This is an important concept given the potential morbidity of repeated brain biopsy and the limitations of conventional magnetic resonance imaging (MRI). Challenges regarding the choice of cerebrospinal fluid (CSF), plasma, or serum, the technological platforms to utilize and which specific components (cell free DNA, RNA, microRNA, other noncoding RNAs, exosomes, tumor-educated platelets, etc.) remain as very active areas of investigation (26–28).

Repeat biopsy or tumor resection can be beneficial to the patient, including reduction of residual disease, assessment of acquired mutational profile and/or identification of new mutations (29). Timing of reoperation can influence the survival benefit and this should be factored into both retrospective and prospective studies (30). Reoperation may provide time to offer salvage therapies, including stereotactic radiosurgery, and assess their efficacy. However, the extent of re-resection is often limited by patient choice, the neuroanatomic location of the tumor and other considerations, such as risks of (further) neurological impairment, venous thromboembolism and/or other complications. Moreover, repeat biopsy may not provide sufficient tissue for full molecular genetic studies. Yet, this new data may inform the selection of available targeted therapies or enable the application of local therapies, such as oncolytic viruses, at the time of reoperation. The availability of additional genomic and epigenomic data includes the mutational signature associated with temozolomide and determination of tumor mutational burden (TMB). An increased TMB is one factor that may render the patient suitable for therapy with immune checkpoint inhibitors, discussed later in this Perspectives article. Furthermore, reoperation can facilitate eligibility to phase I/II clinical trials of novel targeted therapies or assessment of drug delivery and target inhibition in phase 0 or "window of opportunity" clinical trials (31).

Bioinformatic analyses of databases such as the Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) have yielded numerous studies identifying novel prognostic and/or predictive biomarkers. However, many of these studies lack functional or clinical validation studies or have yet to be studied prospectively in clinical trials. Indeed, many of the molecular subgroups identified from these datasets reveal distinct biologies but are often defined by molecular techniques, such as whole transcriptome profiling, that are not readily applicable to the clinical setting.

NEUROIMAGING AND NEUROSURGERY

The use of chemoradiation and subsequently bevacizumab for adult GBM underscored the importance of identifying pseudoprogression and pseudoresponse, respectively. The Response Assessment in Neuro-Oncology (**RANO) criteria** (32, 33) and more recently **iRANO** (immunotherapy) (34) and **RAPNO** (pediatric) (35–37) working groups have standardized response assessments by neuroradiologists and other clinicians in the settings of both clinical trials and in the neuro-oncology clinic. These assessments have been particularly helpful in clinical trial design, but have less utility for the individual patient as the criteria often involve retrospective assignment of progression which is useful in determining the status of a clinical trial endpoint, but often too late to impact individual patient treatment.

The International Neuroimaging Data-sharing Initiative and others aim to streamline processing of MRI and other neuroimaging data across institutions following standard operating procedures for multi-institutional data sharing. These efforts are providing both neuroscientists and clinicians

from less well-developed countries with access to advanced neuroimaging bioinformatics infrastructure, which can assist with diagnosis and assessment of responses to therapy (38–40). Collaborating approaches to develop segmentation algorithms (e.g. identifying areas of tumor or normal structures), such as the Federated Tumor Segmentation (FeTS) initiative (41), permit pooling of de-identified images and processing analysis tools to vastly improve upon what is possible from a single institution.

Furthermore, **radiomics** and the application of machine learning/artificial intelligence to diagnostic MRI scans has the potential to identify early tumor recurrence/progression, distinguish pseudoprogression from progression (42, 43) as well as to identify imaging signatures that are relatively specific to molecular subgroups of the more common diagnoses in adults (GBM, oligodendroglial tumors, low grade gliomas) (44, 45) and children (low grade gliomas, medulloblastoma, ependymoma, diffuse midline gliomas) (46, 47). While several techniques have been described, none have achieved widespread clinical acceptance for routine use. There remains a significant opportunity for those in the radiomics field to combine efforts and define standard, validated approaches to primary brain tumor imaging that can accurately predict tumor diagnosis as well as tumor progression. Once such radiomic collaboration to develop biomarkers of response is the Radiomics Signatures for Precision Diagnostics (ReSPOND) consortium (48) which, like the FeTS initiative, combines multiple institutional datasets to a much larger pool of data of over 3300 patients. Nevertheless, until these radiomic biomarkers achieve widespread clinical utilization, we are reliant on RANO criteria along with subjective clinical assessments.

Intraoperative MRI has the potential to increase the extent of resection and improve the delivery of local therapy, particularly when combined with direct intraoperative visualization techniques such as 5-aminolevulinic acid (5-ALA) **fluorescence guided surgery** (49, 50). Intraoperative stimulated Raman histology provides a real-time histologic analysis of tissue in under 60 seconds and can help direct the neurosurgeon, for example, to pursue additional biopsies or continue a more aggressive resection for a high-grade glioma (51, 52). **Focused ultrasound** can focally disrupt the blood brain barrier and also improve the provision of local therapies mediated by microbubbles (53, 54). Development of improved radiotracers for detection and/or therapy (theragnostic) of hypoxic, metabolic or specific molecular signatures by combined **PET-CT and PET-MR** systems is a very active area of preclinical and clinical study for intra-axial and extra-axial tumors of the central nervous system. For example, ongoing studies of ^{177}Lu-DOTATATE in meningioma have the potential to change the course of this disease at recurrence (55, 56) (NCT03971461).

RADIATION ONCOLOGY

Proton Beam Therapy (PBT), where available, has become the standard of care for some pediatric brain tumors, especially with the demonstration of improved outcomes with respect to hearing loss, neuroendocrinology and especially neurocognition (57–61). Craniospinal irradiation delivered *via* PBT has the advantages of relative sparing of the esophagus, bladder and bowel. However, although countries including the United Kingdom, Australia and Canada are planning to develop PBT in one or more sites, many developed countries currently lack dedicated proton therapy centers, so children and adults often have to travel very long distances to access this therapy (62). Furthermore, the place for PBT in adults, apart from generally accepted indications such as for chordomas, remains to be determined (63). There has been an observed trend to use PBT for low-grade and high-grade gliomas, the majority of which infiltrate into the surrounding brain parenchyma. Further study is warranted. Other forms of particle beam therapy, such as carbon ion therapy, are being evaluated in several countries for patients with meningiomas and gliomas and may have certain advantages over PBT, such as lower oxygen dependence (64).

Linear accelerators (LINAC) combined with onboard magnetic resonance imaging (MR/LINAC) units are increasing the precision of various radiation therapy modalities with the potential to reduce long-term sequelae. Moreover, these instruments allow for daily adaptation of treatments due to changes to tumor or normal anatomy or based on functional imaging data.

In the clinic, there has been a rising lower age limit to offer radiation to children and young adults with a brain tumor, respectively. Deferring or obviating the need for cranial irradiation in infants (less than 3 years) and young children (less than 10 years) is a very important consideration given the demonstrated impact of radiation on brain growth, development and cognition which continues through adolescence to young adulthood. However, it may be difficult to salvage patients with recurrent/progressive disease with radiation when it is not included in upfront therapies along with surgery and chemotherapy. Whenever possible, clinical trials accompanied by comprehensive neuropsychological and neurocognitive assessments are required when assessing the impact of reduced, delayed or omitted radiotherapy (65). For some patient populations, such as those with brain metastases, where therapeutic interventions often have limited impact on the patient's survival but serve an important palliative role, the use of functional, neurocognitive endpoints takes on a greater significance (66). In trials of glioma patients where intermediate endpoints of progression based are of limited benefit, neurocognitive changes may serve as an early indicator of patient survival (67).

Non-ionizing radiation, such as **tumor treating fields** (TTFields), has shown a survival benefit for patients with newly diagnosed GBM (68) and to be equivalent to salvage chemotherapy for patients with recurrent GBM (69). Ongoing trials to combine TTFields with standard and novel therapies are being conducted in both adult and pediatric patients with brain tumors. Despite these results, ongoing concerns raised by some in neuro-oncology has limited its widespread adoption (70). However, recent positive clinical trials in other disease sites only highlight the role of TTFields in the oncologic armamentarium (71).

CHEMOTHERAPY, TARGETED AND EPIGENETIC THERAPIES

The standard of care for newly diagnosed adults with glioblastoma, especially those with MGMT promoter methylated tumors, remains chemoradiation with temozolomide followed by 6 to 12 cycles of adjuvant temozolomide (72). However, the neuro-oncology community is eagerly awaiting a significant advance, especially for those with IDH wild-type MGMT promoter unmethylated tumors. A recent meta-analysis assessed the prognostic value of various MGMT promoter methylation tests for predicting overall survival in temozolomide treated GBM patients. Although both pyrosequencing and methylation specific polymerase chain reaction were superior to immunohistochemistry, determination of ideal thresholds and which specific CpG sites to assess remain undetermined (73).

Furthermore, there is no consensus with respect to the sequence and selection of chemotherapy and/or targeted therapies for recurrent GBM. However, the recent introduction of **IDH inhibitors** in advanced gliomas has demonstrated the importance of identifying molecular subgroups that can benefit from targeted therapies (74). The identification of less common GBM molecular subgroups with fusions involving FGFR or the TRK family of neurotrophin receptors has been another promising advance leading to ongoing clinical trials using fibroblastic growth factor receptor (**FGFR) or tropomyosin receptor kinase (TRK) inhibitors**, respectively (75–77). Similarly, the use of v-Raf murine sarcoma viral oncogene homolog B (**BRAF) inhibitors** for tumors harboring BRAF V600E mutations, including pediatric low grade gliomas, gangliogliomas, pleiomorphic xanthoastrocytomas and Langerhans Cell Histiocytosis, has extended survival for many of these patients (78). A novel approach targeting protein arginine methyltransferase 5 (PRMT5), including a brain-penetrant **PRMT5 inhibitor**, has shown promise in preclinical studies wherein a specific splicing signature in GBM may predict responses to this drug class *in vitro* and *in vivo* (79).

The demonstration that pilocytic astrocytomas are driven by MAPK signaling has resulted in the implementation of **BRAF and/or MEK inhibitors** at the time of initial diagnosis or at progression (78). However, similar to the treatment of recurrent GBM in adults, the timing, sequence and/or duration of the use of these targeted therapies in children requires further study in carefully designed clinical trials, including separate cohorts for patients with neurofibromatosis (NF) type 1. The effect of long-term inhibition of MAPK signaling on normal growth and development of the child remains undetermined. Furthermore, there still remains a place for single agent or combination chemotherapy for these relatively common pediatric brain tumors.

Advances in our understanding of the molecular genetics of diffuse midline gliomas and high-grade gliomas in children have identified the coopting of neurodevelopmental pathways by these tumors and underscore the importance of harnessing **epigenetic-based therapies**, including but not limited to selected HDAC, bromodomain and other inhibitors (80–82). Posterior fossa type A (PFA) ependymomas (83, 84) also demonstrate loss of Histone H3 K27 trimethylation and may benefit from the implementation of these treatments. Challenges are considerable, including tumor specificity, and international cooperative groups are focused on early phase clinical trials to identify promising agents to advance to larger patient cohorts.

CLINICAL TRIAL DESIGN

As former diagnostic categories are parsed into subgroups based upon molecular genetic and other diagnostic considerations, the field of neuro-oncology continues to explore other types of clinical trial design. These include **basket trials** where several diagnostic entities sharing the same mutational profile or target are grouped. **Umbrella trials** or **master protocols** allow larger groups of patients, for example adult GBM, to be enrolled in concurrent and/or sequential smaller phase II trials as part of one very large study that can more efficiently assess the efficacy of novel, often targeted therapies, either at diagnosis or at the time of tumor progression. Adaptive, Bayesian and other innovative clinical trial designs that optimize patient eligibility or use data from prior clinical trials are essential to rapidly translate progress from the basic laboratory to the clinic to improve patient outcomes (85–87). The ongoing Adaptive Global Innovative Learning Environment for Glioblastoma (GBM AGILE) trial combines adaptive trial design with a registration expansion cohort for rapid evaluation of candidate therapeutics and regulatory approval while minimizing the required patient sample size (88). A unique feature of GBM AGILE is the direct incorporation of molecular classification (namely MGMT promoter methylation status) into the trial and the potential for incorporation of treatment-specific predictive molecular biomarkers. This type of adaptive trial is a model which is applicable across neuro-oncology.

IMMUNO-ONCOLOGY

It has been a very exciting time for innovative approaches using several types of therapy that harness the immune system, either alone, in combination or added to standard therapies using chemotherapy or radiation therapy (89, 90). These approaches include **tumor vaccines** (91), **oncolytic viruses** (92–96), **immune checkpoint inhibitors** (97–99) and chimeric antigen receptor (**CAR) T-cells** (100–103). Improved clinical outcomes using immune checkpoint inhibitors in patients with biallelic mismatch repair deficiency and high tumor mutation burdens (TMB) have been reported (104). However, many pediatric and some adult brain tumors have low TMB and are highly immunosuppressive. Recent negative reports of phase III trials of immune checkpoint inhibitors in GBM highlights this challenge (105, 106). Moreover, the use of immunotherapies is complicated by the potential for intracranial inflammation which may result in significant morbidity or long-term complications. Treatment of inflammation using standard corticosteroid therapy can further compound the tumor immunosuppression and negate any benefit from immunotherapy.

Other factors under active study include assessment of the immune tumor microenvironment and how modulating the tumor microenvironment may improve the efficacy of these immunotherapies. Moreover, the influence of the variably intact blood brain barrier and the unintended adverse consequences of immunotherapy, such as brain edema, aseptic meningitis, encephalitis, or peripheral neuropathies are also important considerations as this very promising area of therapy is further developed.

AWARENESS, EQUITY, DIVERSITY AND INCLUSIVITY

In both developed and developing countries there are initiatives to raise public awareness of brain tumors, including the HeadSmart program in the United Kingdom (107). Access to emerging diagnostic (genomic platforms, DNA methylation profiling, advanced imaging) and therapeutic options (targeted and immunotherapies, PBT) remains limited to some developed countries or specific tertiary/quaternary pediatric or comprehensive cancer centers leading the vanguard in neuro-oncology (108). Moreover, it will be challenging for health care systems or third-party insurers in many countries to ensure equitable access to these recent and emerging clinical advances.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

This submission is a Perspective article for World Cancer Day 2021 submitted by DE and ES who equally contributed to the submission. All authors contributed to the article and approved the submitted version.

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