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Getting Personal: Head and Neck Cancer Management in the Era of Genomic Medicine

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Abstract

Background—Genetic testing is rapidly becoming an important tool in the management of patients with head and neck cancer. As we enter the era of genomics and personalized medicine, providers should be aware of testing options, counseling resources, and the benefits, limitations and future of personalized therapy.

Methods—This manuscript offers a primer to assist clinicians treating patients in anticipating and managing the inherent practical and ethical challenges of cancer care in the genomic era.

Results—Clinical applications of genomics for head and neck cancer are emerging. We discuss the indications for genetic testing, types of testing available, implications for care, privacy/disclosure concerns and ethical considerations. Hereditary genetic syndromes associated with head and neck neoplasms are reviewed, and online genetics resources are provided.

Conclusions—This article summarizes and contextualizes the evolving diagnostic and therapeutic options that impact the care of patients with head and neck cancer in the genomic era.

Keywords

Ethics; Head and Neck; Genomics; Cancer; Personalized Medicine

Introduction

Head and neck cancer is the sixth most common cancer worldwide[1]. While smoking, alcohol consumption, and HPV infection are well-established causes, genetic factors play a crucial

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role in tumor initiation, progression, and response to treatment[2]. The vast majority of head and neck cancers are sporadic, with many implicated genetic mutations, making standardized treatment regimens and therapeutic targeting challenging.

Genetic testing is rapidly becoming an important tool in the diagnosis and management of patients with head and neck cancer. What began as basic science initiatives with only theoretical impact has matured into an exciting translational arena in which research and clinical care truly intersect in real-time. In our field, we are approaching a watershed. New genes and pathways serving as potential prognostic indicators or drug targets are being identified at an increasing rate[3–5], and the therapeutic applications, while still in development, have the potential to be ground breaking[6,7].

With such growth, however, come new and unanticipated challenges. As we begin to navigate these waters, it is becoming increasingly important for head and neck cancer specialists (surgeons, medical oncologists, radiation oncologists, researchers and others) to learn about advances in genetics and genomics, the implications of genetic testing for patient care, and potential ethical issues. Providers need to become versed in when to test, when to refer, and where to find genetics resources for their patients. As exciting as new developments are with regard to personalized medicine and the genomic frontier, we need to be ever mindful of the potential unanticipated harm and ramifications they also create. We may risk pursuing unnecessary workup and even potential treatment for genetic alterations that may not necessarily result in disease [8,9]. Moreover, in this era of rapidly changing treatment paradigms, we need to be cognizant of potential conflict between beneficence (the obligation to do good) with autonomy (allowing for patient self-determination and avoiding coercion). Given our commitment to improve care and the allure of novel therapies, we must carefully balance goals and limit harms while respecting patient choices[10].

Head and neck cancer specialists will encounter specific practical and ethical issues in all phases of genetic testing and personalized medicine delivery. This will invariably include 1) initial determination of the indications for and type of genetic testing; 2) provision of genetic counseling so that patients can make an informed choice; 3) interpretation and disclosure of findings; 4) translating results into clinical care; and 5) advising patients, when indicated, about disclosure of results to at-risk relatives. This article is designed as a primer to assist clinicians treating patients with head and neck cancer in anticipating and managing these challenges as we enter the genomic era of cancer care.

Who, Why, and When to Test

Indications for Testing

The first fundamental question most head and neck cancer providers will encounter regards which patients merit genetic testing. The primary indications for testing include the identification of tumor mutations to direct targeted therapy, and recognizing germline mutations that may put patients and/or relatives at risk for head and neck cancers. Most commonly, patients will present with a biopsy-confirmed malignancy of the head and neck. Some patients may express interest in, and/or be candidates for, observational and/or interventional research trials. Genetic testing in these cases is usually performed to identify

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somatic mutations in the tumor tissue to inform correlative research exploring prognostic predictors and/or therapeutic targets[11]. Patients with specific phenotypes or clinical presentations may be targeted for such testing in an effort to identify potentially novel oncogenic drivers or lost suppressors.

A minority of patients might have previously undergone germline genetic testing through blood sample analysis, possibly because of a positive personal and/or family history suggestive of a hereditary syndrome (such as multiple affected individuals, early age of onset, and/or multiple primary cancers). Given the possibility of mosaicism, tumor testing may also be performed in patients with a suspected hereditary cancer syndrome and negative germline testing results. Rare, heritable conditions increasing the risk of head and neck cancers are listed in Table I[12].

Other patients may have been referred due to secondary (also known as incidental) genetic test results that might imply a predisposition for head and neck cancer; these are discussed in depth in ensuing sections. The counseling process for such patients will be fundamentally different compared to a patient with a known or suspected malignancy, and will need to be tailored accordingly.

Testing Options

Physicians have a variety of genetic testing options. Genetic testing to inform the clinical prognosis and/or guide treatment of head and neck cancer is not currently routinely performed. However, testing to identify or screen for targetable mutations is increasingly being used in the research setting. Testing modalities (even for the same gene/condition) vary widely, and therefore selection of the specific genetic test, methodology and laboratory is important. Testing options can range from single gene testing to gene panels to whole exome or whole genome sequencing. Whole exome sequencing refers to sequencing the protein-coding exons in a patient's genome whereas whole genome sequencing involves sequencing coding and non-coding regions of the genome[21]. Analysis of genes can include gene sequencing, mutation panels, deletion/duplication analysis or testing for a known familial gene mutation. Choosing a specific test incorporates clinical judgment and treatment goals. For example, single gene testing for *RET* mutations is appropriate for a patient with a family history of hereditary medullary thyroid cancer, whereas one might employ whole exome/genome or gene panel testing to identify potential targetable mutations in a patient with advanced HNSCC refractory to current care.

Some genetic testing laboratories offer the option of banking DNA or RNA samples from a patient. In situations where the patient has limited lifespan and genetic testing is either not available, too costly or of limited sensitivity, the head and neck cancer provider can offer DNA and RNA banking for future genetic study[22].

Tumor Versus Germline Mutations

Clinicians must clearly distinguish the difference between mutations identified in tumor specimens versus germline mutations. Sequencing tumor DNA can yield a number of mutations that generally will not be found in the individual's germline tissue[23]. Indeed, recent studies in HNSCC have identified an average of 140 mutated genes per tumor

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genome[5]. Counseling patients regarding the implications of mutated tumor genes (which are likely not mutated in their germline cells) should include caveats that such mutations are not heritable, and may have uncertain implications for prognosis and treatment.

Although whole exome or genome sequencing is not currently incorporated in the standard of care for treatment of head and neck cancers, it is increasingly being employed in research settings, primarily to identify prognostic predictors and candidate genes for drug targeting. In these instances, clinicians must clearly distinguish the difference between mutations identified in tumor specimens versus germline mutations. Genetic sequencing of malignant tumor cells involves studying biopsy tissue or an extirpated surgical specimen, and identifying mutations that may contribute to tumorigenesis, predict prognosis and/or represent potential therapeutic targets. In order to identify unique oncogenic mutations, germline genomic DNA is sequenced and used as a background from which mutational changes in tumors are identified. Sequencing germline samples involves non-pathologic cells from patients (usually adjacent normal tissue, or blood)[3,4]. Usually germline DNA is not examined for mutations, but rather is used as the “normal” control[23]. Thus, investigators may be blinded to the germline mutational data. This means of analysis can protect patients from secondary findings, and providers from needing to interpret such data as discussed below. In the rare instances that hereditary head and neck cancer is suspected in a patient, germline genomic DNA may be sequenced in an unblinded fashion. Alternatively, patient genomes can be compared against a reference genome database of pooled sequenced genomes[24] to account for potential known benign and pathogenic variants[25].

Direct to Consumer Testing

Direct-to-consumer (DTC) companies offer genetic screening, which include genes known to be associated with cancers [26]. These tests are ordered by individuals via the internet and usually without the involvement of a physician. These companies identify single nucleotide polymorphisms (SNPs), and offer proprietary assessments on risk for a number of diseases based upon these findings, including risk for cancer. Risk assessment and disease prediction based on SNPs is of limited clinical utility, and could result in misinformation or false reassurance. Patients may present to clinicians with such pre-interpreted data and have ensuing questions and concerns. Knowledge of the limitations and means of interpretation will be important for the provider tasked with discussing DTC results with these patients. It is important to inform patients that these direct-to-consumer tests are not considered standard of care, do not have external quality control, are not ordered in genetics clinics, and may have limited clinical validity[27–30].

In 2013, the FDA issued a cease and desist order against 23andme due to concerns with the accuracy and validity of their interpretations with clinical implications, including cancer risk[27]. The American College of Medical Genetics and Genomics (ACMG) and the National Society of Genetic Counselors recommend involvement of a geneticist or genetic counselor to discuss issues regarding indications for and interpretation of testing[28,29]. This includes discussing the limitations of results, having easy to understand information available, and ensuring proper lab accreditation[28,30]. Thus, DTC services remain in flux and have significant limitations about which physicians should inform patients accordingly.

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Pre-test Counseling

Regardless of clinical context, it is important to have a clear and definitive consent process in which the implications of testing are clearly addressed[31,32]. Genetic test results have broad implications. Issues to discuss include testing options, the likelihood of identifying the gene mutation(s) and whether additional testing might be needed, the types of results and implications, cost of testing, and privacy and insurance considerations. Explicit and comprehensive pre-test counseling has been strongly recommended by the American Society of Clinical Oncology (ASCO) as an integral component of the consent process[32].

Head and neck cancer specialists may see patients who either have (or are at increased risk for) cancer and need to consider genetic testing and/or have results interpreted. Debate exists whether any care provider may interpret and provide counseling on results of genetic testing, or whether this should be a role reserved specifically for geneticists and genetic counselors[33]. There have been reports of adverse outcomes with clinicians without dedicated training providing cancer genetics counseling to patients[9].

The wide array of testing options can be overwhelming for patients and providers alike. Moreover, insurance coverage of genetic testing is often a major hurdle for patients, and costs of such tests may be exorbitant. Given the expertise needed to select the specific gene(s), testing methodology and laboratory, as well as to provide accurate result interpretation, it is generally recommended that patients be referred to a cancer genetics clinic, an oncology clinic with a genetic counselor, or a specialist with genetics expertise. Resources for finding providers with genetics expertise and other genetics resources for patients and providers are included in Table II[34]. Telephone or internet-based genetic counseling services are also available, which may provide an alternative avenue for patients with limited geographic access.

Privacy Concerns

Patients may have concerns about the privacy of genetic information and the implications results could have for their insurance coverage. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) specifically incorporates genetic information in its protection of patients' clinical data[35]. The HIPAA/HITECH Act was updated in 2013 to confirm that a person's genetic information is indeed considered protected health information, and cannot be disclosed without a patient's explicit written consent[36]. Genetic information in these cases includes family medical history, individual and familial genetic test results.

In 2008, the Genetic Information Nondiscrimination Act (GINA) was passed into law. The purpose of this act is to prevent discrimination based upon one's genetic information[37]. The act prevents health insurance companies (private and public) from being able to request genetic testing as a condition for eligibility or insurability, and prevents discrimination in premiums based upon known genetic test results. Additionally, the law prohibits employers from requesting or using genetic information for employment decisions. Notably GINA does not apply to businesses with less than 15 employees. The Affordable Care Act, passed in 2010, reinforced these principles; it does not allow health insurers to vary insurance rates or

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coverage due to pre-existing conditions, including genetic disease or results[38]. GINA has been strongly enforced, with the U.S. Equal Employment Opportunities Commission recently reaching two settlements against companies requesting family medical information on the grounds that patients' genetic rights were being violated[39,40].

Of note, life, long-term care and disability insurance are currently not protected; patients with known gene mutations may have more difficulty obtaining such insurance policies and should be counseled accordingly prior to testing[37]. Information on GINA and legislation regarding the use of genetic information in insurance and employment can be accessed through the resources listed in Table II.

Consent allowing for the future research use of banked specimens in the clinical or research arena may raise unforeseen privacy concerns in ensuing years. These privacy issues are an integral component of the pre-test consent process. As such, patients should receive assurance regarding how samples and genetic test results will be protected, and how the information can and cannot be shared and utilized. Privacy can be of particular concern with regard to DTC testing, as private companies are not necessarily health providers who are bound by HIPAA, and may not have explicit policies protecting collected data[30].

Testing Children

It is important to carefully consider circumstances surrounding testing of children. While head and neck cancer is generally an adult disease, genetic conditions may place children at risk for head and neck cancers that require early detection and intervention (e.g. medullary thyroid carcinoma; Table I). The American Academy of Pediatrics and ACMG issued a joint statement with the overriding goal of prioritizing the best interests and care of the infant or child, which supports genetic testing only when anticipated results will affect clinical management prior to adulthood[41].

Interpretation and Disclosure of Results

When contemplating genetic testing in head and neck cancer, pre-test counseling can proactively address possible results and their implications. The ACMG recently discussed addressing variants and mutations encouraging use of standardized terminology, including "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign" to convey certainty and risk of disease[42]. These labels should be employed when disclosing such variants.

If exome or whole genome sequencing is being done, an increasingly important and complex issue to address is how to deal with the identification of secondary (incidental) findings of pathogenic mutations or variants of unknown significance for conditions unrelated to the indication for testing. In broad strokes, the consensus amongst most experts favors the disclosure of incidentally found mutations only when (1) they have clinical significance, (2) patients have consented to receive the information, and (3) they are clinically actionable (impacting screening and treatment decisions)[31,43]. While this makes good sense in theory, the significant challenge arises in determining which tests and test results satisfy the first and third stipulations.

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Clinically Significant Incidental Mutations

The ACMG provided a controversial recommendation in 2013 regarding disclosure of secondary (incidental) findings. They published a list of 56 genes with potential clinically actionable impact for which they recommended screening and disclosure in every instance in which a person undergoes germline genomic sequencing[44]. Twenty-three of these genes are related to cancer risk. Of particular interest to the head and neck provider are genes for medullary thyroid cancer (*RET*, *MEN1*), hereditary paraganglioma (*SDHD*, *SDHAF2*, *SDHC*, *and SDHB*), neurofibromatosis 2 (*NF2*), and Li-Fraumeni syndrome (*TP53*), among others (Table I).

Subsequently, there has been intense debate on whether mandating characterization of these 56 genes in genomic studies infringes upon patient autonomy, as many other organizations, including the President's Commission on Bioethics, have emphasized respecting a patient's right *not* to know[45–48]. Some suggest that by mandating screening when a patient is undergoing genomic testing (thereby denying one's right not to know), patient autonomy is compromised in order to achieve a presumably beneficent objective. Others might counter that if the germline DNA is being analyzed, it behooves clinicians and researchers to report on relevant findings, and potentially provide care options[49]. Similar ethical issues frequently arise in other arenas of clinical care, such as incidental findings on imaging[50], with arguments for specific instances for disclosure of "relevant," albeit unanticipated, results. In response to concerns raised in the genetics community, the ACMG softened its stance, with updated recommendations allowing for an "opt-out" option prior to sequencing[51].

Specific pre-test discussion reviewing patient preferences regarding disclosure of both anticipated and secondary findings is important. It remains important to inform patients about the ACMG recommendations and have discussions concerning the benefits and risks of screening these 56 genes, and potentially other genes as well. Broadly speaking, explicit benefits include identifying conditions for which the patient is at increased risk, possible disease prevention through screening or early treatment (e.g. prophylactic thyroidectomy in patients with clinically occult *RET* mutations) and the ability to inform other at-risk relatives. Risks include identifying a mutation that has unknown penetrance in a low-risk population, finding variants of unknown significance with unclear clinical implications, and the emotional impact of learning about risks for other conditions when already dealing with cancer. As the field of genomic research evolves, the knowledge base will expand, and the implications of such findings (and the number of genes for which clinically relevant information becomes available) will only grow exponentially.

Variants of Unknown Significance

Genomic testing uncovers a high number of SNPs and variants of unknown significance (VUS)[52]. The vast majority of SNPs are thought to be non-pathologic allelic variants[53]. Of those that have some association with increased cancer risk, the impact of individual SNPs is believed to be quite low, with odds ratios ranging from 1.2 to 1.6[54]. Variants of unknown significance are identified at a high frequency particularly in HNSCCs, where these tumors average 140 genes containing at least one somatic mutation[5], and with many of these

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mutations unique and previously unreported. Consequently, the functional outcomes of these mutations are largely unknown.

Interpretation and disclosure of SNPs and VUS is a complex process. Reporting all of these variants will obviously be overwhelming and difficult to interpret for providers, let alone patients. Additionally, the clinical utility of these findings is limited. Unlike in cases of a highly penetrant pathological mutation, any consideration regarding disclosure of information regarding SNPs should be prefaced by an acknowledgment of their limited clinical utility. It should be clearly conveyed during pre-test counseling and disclosure to patients that a VUS truly has unknown significance, should not be equated to a pathogenic mutation, and may be reclassified as more is learned in the future. As such, disclosure of VUS identified through genomic sequencing in genes unrelated to the primary disease process is not routinely performed. In instances when the clinician and patient agree to disclosure, these variants should be classified based on suspicion of pathogenicity, as described above[42].

Clinically Actionable Findings

When considering disclosure, a key debate centers on what makes a particular finding "clinically actionable"[8,43]. Offit et al[55] highlighted the importance of distinguishing clinical diseases with high versus low gene penetrance, and actionable versus non-actionable results. One must consider, however, that as our ability to treat disease rapidly evolves, what is not "clinically actionable" at this time may very well become so in the near future. Thus, continual reassessment of our knowledge base, clinical recommendations and disclosure should be performed. Patients should also be encouraged to remain in touch with their providers to continually reassess the implications of their clinical data.

Specifically, clinically actionable results are those for which an intervention may be performed to screen for pathology, prevent or eliminate disease, or improve patient outcomes. For example, neoplasms with discrete genetic causes impacting the head and neck include medullary thyroid cancer (*RET*). For patients with germline *RET* mutations, American Thyroid Association guidelines have strict criteria for mutation-specific screening and management, including prophylactic thyroidectomy in certain cases[14]. As another example, patients with hereditary paragangliomas (*SDHAF2*, *SDHD*, *SDHC*, *SDHB*) have specific indications for imaging, screening family members, and intervention[16].

Some diseases with genetic associations may be clinically relevant, but not clinically actionable. The concept is illustrated by using Huntington's disease as a paradigm. Informing a patient about a risk for Huntington's disease does not lead to a change in clinical outcome but has significant prognostic and psychological ramifications. Some patients would request such results, whereas others would never want to know. International guidelines detail the comprehensive pre-test counseling, informed consent and in-person disclosure of genetic test results for Huntington's disease[56].

The Duty to Warn

Our discussion to date has been patient-centric, and rightfully so; the primary concern in all such cases is the rights and well-being of the individual who has entrusted his or her health

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to your care. However genetic information necessarily transcends the doctor-patient dyad. As such, the perspective and rights of family members also require attention and discussion. There is an inherent conflict between patients' rights to privacy and ownership of information, with the duty to share relevant facts with their family. In the majority of cases, patients who are appropriately counseled will agree to involve family as is necessary in order to inform their own healthcare choices. However this may not always hold true. Hence, clinicians may be placed in situations where they must weigh the relative importance of one patient's autonomy and privacy, versus the duty to shepherd the interests of their relatives[57–59].

Pre-test counseling should include discussing the significance and implications of results for family members. But what should be done in the rare cases in which a patient's request conflicts with familial best interests despite adequate counseling? The American Medical Association and ASCO do not sanction physicians to override patient confidentiality in order to warn family members[60,61]. The American Society of Human Genetics advocates that physicians have the responsibility to warn at-risk family members only if the potential harm is imminent and serious, and treatment or prevention options are available[59]. The legal basis for the latter position is an extrapolation of the well-known Tarasoff ruling (1976)[62], in which physicians can override confidentiality and are obligated to warn at-risk third parties of imminent danger. Briefly, in the Tarasoff case, a psychologist treated a patient who expressed intent to kill a third party; no warning or alert was given to the victim, and the patient ultimately carried out his plan. The California Supreme Court subsequently established legal precedent for a clinician's duty to warn third parties against overt threats, clarifying that danger to others may override confidentiality.

Lawsuits have been filed in cases where physicians did not explicitly warn family members of their risk of developing a heritable cancer. Pate v Threlkel (1995)[63] is of particular interest to head and neck providers, as this case involved a patient whose mother was previously treated for medullary thyroid carcinoma. The plaintiff developed the disease years later, and filed suit claiming that her cancer could have been avoided with earlier screening and prophylactic thyroidectomy. The court ruled in favor of the defendant, claiming that the physician's duty to warn was sufficiently fulfilled by discussing potential risks affecting family members with the patient, rather than seeking family members directly. Another relevant case, Safer v Estate of Pack (1996)[64], offers a conflicting interpretation. Involving a case of familial adenomatous polyposis, the court held that a physician's duty to warn family members may not be satisfied just by alerting the patient, but rather a physician may need to take extra steps to warn such individuals directly. Ultimately, the New Jersey appellate court sided with the defendant. Although a patient's HIPAA-protected confidentiality remains important, in this instance, the court ruled that disclosure was justified.

As evidenced by conflicting professional guidelines and case law, the ethics and legalities governing the disclosure of genetic information to family members remains an extremely complex issue. The interested reader is referred to more robust discussions of this topic as further details are beyond our scope[55,57]. In summary, pre-test discussions will necessarily include counseling regarding potential impact upon family members, and clinicians are

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behooved to consider the impact of information on individuals other than the patient sitting in front of them. In cases involving conflicting obligations concerning access to information and privacy, ethics and/or legal consultation is strongly encouraged.

Translating Genomics into Treatment

As we enter an era of personalized medicine and targeted therapies, genomic characterization is playing an increasingly larger role in how we individualize cancer treatment[65–67]. It remains important to note that personalized medicine and genomic testing are currently not standard of care in head and neck cancer management. As it now stands, there is no genomic signature that influences the routine guideline-based treatment of head and neck squamous cell carcinoma. In fact, to date, the FDA has only approved 19 companion diagnostic tests for use in the treatment of cancer[68]. However, genomic studies are an instrumental component of translational research programs, and will likely become integrated into routine clinical care in the near future as the field advances. With regard to targeted therapies, while cetuximab is currently the only FDA-approved targeted agent in the management of head and neck squamous cell carcinoma[69,70], numerous exciting targeted therapies are in various stages of development[6]. There have been significant advances in targeted therapy against thyroid cancer. Sorafenib (Nexavar) and lenvatinib (Lenvima) have shown survival benefit and are FDA-approved for locally recurrent or metastatic differentiated thyroid cancer refractory to radioiodine therapy[71,72]. Additionally, there are FDA-approved targeted therapeutics [vandetanib (Caprelsa) and cabozantinib (Cometriq)] for unresectable, progressive, or metastatic medullary thyroid cancer [73,74].

Even in the face of encouraging preclinical data and/or extrapolated results from other cancers, counseling patients for genomic screening to select targeted therapy needs to emphasize the investigational nature of these studies. A high level of caution is necessary prior to offering an unproven targeted agent based upon genomic findings. Conflict may arise in situations in which a patient has identified mutations in potentially targetable genes, with agents with unproven responses in head and neck cancers. The value of attempting novel therapies versus the standard of care must be carefully weighed in such cases. Our opinion is that any use of genomic data to inform cancer-directed therapy in the head and neck (either with curative or palliative intent) should be reserved for patients meeting strict inclusion criteria, and governed by a clear experimental clinical research protocol with IRB oversight, with a comprehensive informed consent process.

We feel that this is especially critical in genetically complex cancers, such as smoking and alcohol-related HNSCC. Unfortunately, when targeted monotherapies fail in precision medicine clinical trials, the recurrent tumors can be highly aggressive and rapidly lethal. Due to the complex array of disruptive genomic events in HNSCC, it is unlikely that individual targeted monotherapy with currently available agents will produce significant response. In these cases, it may be appropriate to consider ongoing clinical trials of complex combinations targeting multiple drivers that have been evaluated in phase I safety trials.

Another important factor in consideration of HNSCC treatment is HPV status. It is well established that HPV-associated HNSCCs have a better prognosis than their HPV negative

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counterparts, and consist of a different epidemiological group (HPV versus smoking and alcohol related tumors)[75]. Moreover, HPV positive tumors appear to have a lighter mutational burden in comparison to HPV negative HNSCCs[5,76]. In light of these significant mutational, biologic and outcome differences, discrete personalized treatment paradigms may be developed based in part upon HPV status[6].

In general, the ideal patients for early phase trials involving targeted personalized therapy may include those with recurrent/persistent/incurable disease who have not responded to current standard of care, or those with rare tumors for which no standard treatment may exist. We strongly encourage head and neck cancer clinicians and patients alike to consider enrolling in ongoing trials (both observational and interventional) within dynamic multidisciplinary translational research programs. Such involvement is critical in guiding further care due to the nascent nature of the field and need for more robust data designed to understand the investigational nature of targeted therapy based upon genomic results.

Multidisciplinary involvement from head and neck surgeons, geneticists, medical and radiation oncologists, and translational biologists is integral to developing personalized treatment paradigms. Genomic data may be discussed at Precision Medicine Tumor Boards to identify potential trials using targeted agents in which the patient may enroll. The National Cancer Institute and many tertiary care centers throughout the country are creating such programs using genetic information to apply personalized, targeted therapy to selected cancers[77,78]. Their growing relevance speaks to the excitement of cancer care in the era of genomics.

It should be clearly explained during the consent process to patients enrolling in early phase clinical trials that the primary goal of these trials is to establish drug dosing, feasibility of treatment, and to document adverse effects. While patients, clinicians and researchers alike will necessarily be hopeful for clinical response or cure, this is NOT necessarily the primary outcome, nor the reason such early phase trials were designed. Such patients are extremely vulnerable to therapeutic misconception (the misunderstanding about the difference in goals between clinical research versus treatment)[79]. This point should be stressed as patients have been shown to be prone to have overly optimistic expectations of beneficial results from investigational treatments or treatment therapies for advanced cancer despite rigorous informed consent processes[80–82]. Open discussion of potential conflicts of interest and the discrete goals of patients, families, clinicians and researchers should be openly disclosed to identify potential areas of contention or confusion.

Conclusion

The era of personalized medicine has arrived. No longer do cancer genomic researchers study anonymous cells devoid of a corresponding patient. Likewise, head and neck cancer specialists cannot ignore the rapid advances made in laboratories across the world, as these findings will fundamentally shape our interactions at the bedside. In this setting, clinicians treating head and neck cancer must become familiar with genomic medicine. As genomic advances inform head and neck oncology, guidelines on the use of and ethics inherent to genetic testing in diagnosis and management will need to be developed and take into account

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the constantly evolving nature of the field. The ethical issues arising from the concept of genomics and personalized medicine include conflicts between autonomy and beneficence, communication and management of secondary findings, how to appropriately design and conduct trials with individualized targeted medications, privacy concerns and considering the duty to warn. Head and neck cancer specialists must become literate in the language, scope and practice of personalized medicine resources, both to remain at the forefront of cancer treatment as well as to continue to support the best interests and rights of our patients.

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Table I

Hereditary Genetic Syndromes Associated with Head and Neck Neoplasms

Condition	Tumor Type	Gene	Inheritance	Incidence	Guidelines
Ataxia Telangiectasia	BCC	*ATM*	AR	1:40,000–100,000	No
Bloom	Esophagus, Larynx, Tongue, SCC, BCC	*BLM*	AR	1:50,000 Ashkenazi Jews	No
Carney	Thyroid (non-medullary), Schwannoma	*PRKAR1A*	AD	Unknown (rare)	No
Chordoma	Chordoma	*T*	AD	1:1,000,000	No
Cowden	Melanoma, Thyroid (non- medullary), Thyroid (medullary)	*PTEN**, *SDHB**, *SDHD**, *KLLN*	AD	1:200,000	Yes[13]
Dyskeratosis congenita	Tongue, Esophagus, HNSCC	*TERT, TERC, DKC1, TINF2*	AD, AR, XLR	1:1,000,000	No
Familial Adenomatous Polyposis	Thyroid (non-medullary), Juvenile Nasopharyngeal Angiofibroma	*APC**, *MUTYH*	AD	1:7,000–22,000	No
Familial Medullary Thyroid Cancer	Thyroid (medullary)	*RET**, *NTRK1**	AD	1:35,000 (MEN2)	Yes[14]
Fanconi	SCC	Multiple (*FANCA, FANCB, FANCC*, etc).	AR, XLR	1:160,000 (more common in Ashkenazi Jews)	Yes[15]
Gorlin	BCC	*PTCH1*	AD	1:31,000	No
Hereditary Breast Cancer	Larynx, Melanoma	*BRCA2**	AD	1:400 (BRCA1/2), 1:40 Ashkenazi Jews (BRCA 1/2)	No
Hereditary Paraganglioma Syndrome	Thyroid (non-medullary), Paraganglioma	*SDHAF2**, *SDHD**, *SDHC**, *SDHB**	AD	1:1,000,000	Yes[16]
Hyperparathyroidism-Jaw Tumor	Parathyroid carcinoma, Ossifying fibroma	*CDC73*	AD	Unknown (rare)	No
Li-Fraumeni	Larynx, Melanoma	*TP53**, *CHEK2*	AD	Unknown (rare)	No
Multiple Endocrine Neoplasia, Type 1	Parathyroid, Thyroid (non-medullary)	*MEN1**	AD	1:30,000	Yes[17]
Multiple Endocrine Neoplasia, Type 2	Parathyroid, Thyroid (non-medullary), Thyroid (medullary), Paraganglioma	*RET**	AD	1:35,000	Yes[14]
Multiple Endocrine Neoplasia, Type 4	Parathyroid	*CDKN1B*	AD	Unknown (rare)	No
Neurofibromatosis, Type 1	Paraganglioma, Neurofibroma, Schwannoma	*NF1*	AD	1:3,000–4,000	Yes[18]
Neurofibromatosis, Type 2	Vestibular Schwannoma, Neurofibroma	*NF2**	AD	1:33,000	Yes[19]
Retinoblastoma	HNSCC, Melanoma	*RB1**	AD	1:10,000–14,000 in children 0–4	No
Rothmund-Thomson	HNSCC, BCC, SCC	*RECQL4*	AR	Unknown (rare)	No

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Condition	Tumor Type	Gene	Inheritance	Incidence	Guidelines
Tuberous Sclerosis	Chordoma, Thyroid (non-medullary)	*TSC1*[*], *TSC2*[*]	AD	1:6,000	No
von Hippel-Lindau	Paraganglioma, Endolymphatic sac tumors	*VHL*[*]	AD	1:36,000	Yes[20]
Werner	BCC, Melanoma, SCC, Thyroid (non-medullary)	*WRN*	AR	1:200,000 (more common in Japan)	No
Xeroderma pigmentosum	HNSCC, BCC, SCC, Melanoma, Tongue	*XPC, XPA, ERCC2, ERCC3, POLH*	AR	1:1,000,000 in US, Europe (more common in Japan, Africa, Middle East)	No

[*] = Gene recommended for screening by ACMG

BCC = Basal cell carcinoma; SCC = Cutaneous head and neck squamous cell carcinoma HNSCC = Mucosal head and neck squamous cell carcinoma; AD = Autosomal dominant AR = Autosomal recessive; XLR=X-linked recessive

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Table II

Online Genetic Resources

Online Searchable Databases of Genetic Specialists and Genetics Clinics
• American Board of Genetic Counseling (“Find a Certified Genetic Counselor”) • American College of Medical Genetics and Genomics (“Find Genetic Services”) • GeneClinics (GeneTests website, follow link to “Clinics”, includes clinics in other countries) • National Cancer Institute - Cancer Genetics Services Directory • National Society of Genetic Counselors (“Find a Genetic Counselor”) • Orphanet (clinics in Europe)
Information about Genetic Conditions for Healthcare Professionals
• GeneReviews • MedGen (NCBI) • National Cancer Institute: PDQ Cancer Information Summaries - Genetics • Online Mendelian Inheritance in Man (OMIM) • Orphanet
Information about Genetic Conditions, Genetic Testing and Support Group Resources for Patients
• Genetics Home Reference • Genetic Alliance (“DiseaseInfo Search” link to find support groups for genetic conditions) • Genetic Alliance UK • Genetic and Rare Diseases Information Center (has phone option) • National Organization for Rare Disorders • Orphanet (support group resources in Europe)
Fact Sheets/Brochures about Patterns of Inheritance
• Centre for Genetics Education (“Genetics Fact Sheets” link, “Multilingual Resources” link) • EuroGenTest (“Patient Leaflets” link; multiple languages) • Genetic Alliance UK (“Information Centre” link; multiple languages)
Genetic Testing (insurance implications information)
• Genetic Information Nondiscrimination Act (GINA): www.ginahelp.org • National Human Genome Research Institute – Genetic Discrimination – Genome Statute and Legislative Database • HumGen (international database)
Genetic Testing (general information)
• Genetics Home Reference (“Handbook” link) • National Cancer Institute – Fact Sheet: Genetic Testing for Hereditary Cancer Syndromes • National Human Genome Research Institute: – Frequently Asked Questions about Genetic Testing

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– “Genetic Testing: What it Means for your Health and for your Family’s Health
Online Searchable Databases of Genetic Tests
• Genetic Testing Registry – NCBI (GTR) • GeneTests • Eurogentests (Clinical Utility Gene Cards, labs in Europe) • Orphanet (labs in Europe)