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Review

REVIEW

The Conundrum of Genetic "Drivers" in Benign Conditions

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Abstract

Advances in deep genomic sequencing have identified a spectrum of cancer-specific passenger and driver aberrations. Clones with driver anomalies are believed to be positively selected during carcinogenesis. Accumulating evidence, however, shows that genomic alterations, such as those in *BRAF*, *RAS*, *EGFR*, *HER2*, *FGFR3*, *PIK3CA*, *TP53*, *CDKN2A*, and *NF1/2*, all of which are considered hallmark drivers of specific cancers, can also be identified in benign and premalignant conditions, occasionally at frequencies higher than in their malignant counterparts. Targeting these genomic drivers can produce dramatic responses in advanced cancer, but the effects on their benign counterparts are less clear. This benign-malignant phenomenon is well illustrated in studies of *BRAF* V600E mutations, which are paradoxically more frequent in benign nevi (~80%) than in dysplastic nevi (~60%) or melanoma (~40%-45%). Similarly, human epidermal growth factor receptor 2 is more commonly overexpressed in ductal carcinoma in situ (~27%-56%) when compared with invasive breast cancer (~11%-20%). *FGFR3* mutations in bladder cancer also decrease with tumor grade (low-grade tumors, ~61%; high-grade, ~11%). "Driver" mutations also occur in nonmalignant settings: *TP53* mutations in synovial tissue from rheumatoid arthritis and *FGFR3* mutations in seborrheic keratosis. The latter observations suggest that the oncogenicity of these alterations may be tissue context–dependent. The conversion of benign conditions to premalignant disease may involve other genetic events and/or epigenetic reprogramming. Putative driver mutations can also be germline and associated with increased cancer risk (eg, germline *RAS* or *TP53* alterations), but germline *FGFR3* or *NF2* abnormalities do not predispose to malignancy. We discuss the enigma of genetic "drivers" in benign and premalignant conditions and the implications for prevention strategies and theories of tumorigenesis.

Cancers are known to arise, at least in part, as a result of acquired changes in DNA, and such changes accumulate over time (1). With the advent of next-generation sequencing (NGS), the full complement of genetic alterations in a given cancer can be identified (2). Some of these abnormalities are "passengers" that do not drive progression to metastatic disease (3). Other alterations, termed genetic "drivers" (4,5), are implicated in pathways crucial to the ability of cancer cells to grow and survive. Clones harboring driver anomalies are presumed to be positively selected in the evolution of neoplasia to invasive and advanced cancer (3). Overall, a basic premise in oncology is that, via the process of clonal selection, driver mutations are rare in benign conditions, variably present in premalignancy (depending on severity and cancer risk), and most frequent in advanced cancer (3,6). Recent studies, albeit limited, have suggested that genetic drivers can occur in early cancer (7) and premalignancy (8–18).

The identification of genetic drivers has resulted in the development of targeted therapies with promising outcomes in patients with advanced cancers that harbor actionable

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alterations (19). In this review, we describe an emerging body of literature indicating that genomic drivers, considered a hallmark of specific cancers, can also be found in benign conditions and in premalignant lesions, sometimes at frequencies higher than in the corresponding tumors (Table 1), and discuss the implications of these findings for current theories of carcinogenesis and designing prevention strategies.

BRAF

BRAF is a member of the RAF kinase family, with CRAF being the more ubiquitously expressed component in physiologic mitogen-activated protein (MAP) kinase pathway signaling (20,21). MAP kinase signaling plays a key role in cell division, differentiation, and survival.

BRAF in Cancer

Mutations in the *BRAF* gene, especially the V600E mutation, lead to constitutive activation of the MAP kinase pathway and increase in growth signals (22). While *BRAF* V600E mutations are present in almost half of patients with melanoma (22–25), they are also found in up to 17% of patients with diverse, advanced metastatic cancers seeking therapy following failure of standard treatments (19). *BRAF* mutations are clinically important targets because they are sensitive to BRAF (26–31) or MAP kinase-ERK kinase (MEK) inhibitors (32).

The *BRAF* V600E mutation has been identified in 40% to 45% of metastatic melanomas in prospective studies with comprehensive interrogation (23,24). This mutation is considered an oncogenic driver, and melanomas bearing these *BRAF* V600E alterations have excellent responses to BRAF inhibitors such as vemurafenib or dabrafenib (26,27); these responses are entirely comparable with the most effective single-agent, oncogene-targeted therapies in non–small lung cancer (EGFR and ALK inhibitors in patients with corresponding actionable alterations) (33–36).

BRAF in Melanocytic Nevi and Dysplastic Nevi

The *BRAF* V600E mutation is very common in benign melanocytic nevi, being discernible in 70% to 88% of such lesions (37,38). It is also found in approximately 60% of dysplastic nevi, with no clear correlation with degree of dysplasia (13); the latter can be a precursor of melanoma. Thus, *BRAF* mutations are considered to be one of the earliest events in melanoma development (39). Curiously, however, less than 0.03% of melanocytic nevi (40) and only about 4.8% of dysplastic nevi transform to melanoma (although risk increases with the number and size of dysplastic nevi and degree of dysplasia) (41). As mentioned, the frequency of *BRAF* V600E mutations is paradoxically lower (40%-45%) (22–25) in melanoma compared with melanocytic nevi (37,39) or dysplastic nevi (13) (Table 1). If *BRAF* mutations were a strong driver for melanoma development, one would assume they would be more commonly seen in patients with melanoma than in its benign counterpart. Because approximately 50% of patients with melanoma with *BRAF* mutations respond to BRAF (26–31) or MEK inhibitors (32), there is no doubt that these melanomas depend on the MAP kinase pathway, but whether oncogenic *BRAF* itself is sufficient to sustain oncogenic MAP kinase signaling is an open question.

A variety of changes have been reported in preexisting, previously stable melanocytic nevi in patients receiving BRAF inhibitors, including increased pigmentation and involution. For instance, Haenssle et al. (42) observed that the BRAF inhibitor vemurafenib could lead to dynamic changes in melanocytic nevi, with both regression or increased size or pigmentation of melanocytic nevi at different sites. The biochemical correlates of these effects have not been elucidated. However, it may be that even in dormant melanocytic nevi BRAF inhibitors increase expression of microphthalmia-associated transcription factor (MITF), with several consequences including upregulation of pigmentation pathways. In contrast, a melanoma with a *BRAF* V600E mutation in the same individual regressed with therapy (42), suggesting the enigmatic conclusion that the *BRAF* V600E mutation in melanoma is a driver while it is not a driver in melanocytic nevi. Furthermore, Cohen et al. observed development of new dysplastic nevi or new primary melanomas when patients were treated with vemurafenib for melanomas with *BRAF* V600E mutations (43). Some melanocytic nevi that were newly developed or had morphological changes observed in patients with melanoma receiving BRAF inhibitor therapy for metastatic *BRAF* V600E-disease have activating *NRAS* mutations (not *BRAF*) and are thought to arise as a consequence of the well-described triggering effect that these agents can have on *RAS*-activated premalignant lesions (44,45).

Despite the dynamic changes described in some benign melanocytic nevi on BRAF inhibitor therapy, for the most part these nevi remain static when a patient is treated with vemurafenib or dabrafenib, even though the vast majority of these nevi harbor *BRAF* V600E "driver" mutations. This dichotomy is difficult to reconcile, but it is possible to postulate that an endogenous inhibitor against BRAF or other constituents of the MAP kinase pathway may exist in melanocytic nevi, hence protecting melanocytic nevi from behaving like a malignancy and from regressing in the face of BRAF inhibitor treatment (tumor-suppressor hypothesis). Alternatively, or in addition, one of more cofactors may need to be mutated in order for transformation of melanocytic nevi to melanoma to occur (second oncogene hypothesis) (Figure 1). In support of both theories, investigation of activated ERK in melanocytic nevi by immunohistochemistry consistently demonstrates low levels of MAP kinase pathway activation (whereas it is uniformly elevated in *BRAF* V600E metastatic melanomas) (46).

In an effort to clarify possible BRAF codrivers, experimental models have been generated with genetic manipulation of tumor suppressors known to be altered in invasive and metastatic melanomas. Patton et al. (47) showed that *BRAF* V600E-mutated zebrafish developed patches of ectopic melanocytes; however, when *TP53* was also deleted, zebrafish rapidly developed invasive melanomas. Using the same *BRAF* V600E-mutant/*TP53*-deficient zebrafish model, Kaufman et al. recently demonstrated that the *crestin* gene is not only expressed in neural crest progenitors (during the embryonic state) but also re-expressed during melanoma development, suggesting that the *crestin* gene is necessary for melanomagenesis. Overexpression of *SOX10* (the neural crest master transcription factor) in melanocytes accelerated the onset of melanoma, indicating that a dedifferentiated, epigenetic state may also play a part in cancer transformation following the appearance of driver genetic alterations (48). In mouse models in which *BRAF* V600E was conditionally expressed in melanocytes, melanocytic proliferations were observed with histologic features of melanoma, but invasive melanomas did not develop (49). In two different models, codeletion of *PTEN* or *CDKN2A* with expression of *BRAF* V600E produced highly penetrant invasive and even metastatic melanomas (49,50).

Table 1. Examples of paradoxically aberrant oncogene drivers in benign conditions, premalignant lesions and their malignant counterpart

Gene	Aberration	Benign or premalignant condition: % with aberration (references)	Malignant condition: % with aberration (references)	Examples of specific mutations found in both benign/premalignant conditions and cancer
BRAF	Mutations	Melanocytic nevi: 70%-88% (37,38) Dysplastic nevi: ~60% (13)	Melanoma: ~40%-45% (22–25) Across cancers:Up to 17% (19)	V600E
*NRAS**	Mutations	Melanocytic nevi: 6%-14% (71,72) Includes Q61K Congenital melanocytic nevi: 70%-95% (73,74) Includes Q61K and Q61R	Cutaneous melanoma: 18%-28% (62,64) Includes Q61 Across cancers: Up to 8% (19)	Q61K, Q61R
GNAQ†	Mutations	Sturge-Weber syndrome: R183Q: 88% (83)	Uveal melanoma: Q209L: 22%-45% R183Q: 3%-6% (84)	R183Q
FGFR3†	Mutations	Seborrheic keratosis: ~18%-85% (102–105) Includes R248C, S249C, G372C, S373C, A393E, K652E, K652M Epidermal nevi: 33% (106) Includes R248C, G372C, G382R	Cervical cancer: 1.7-25% (95,99) Includes S249C Urothelial bladder cancer: 11%-35% (94–96) Includes R248C, S249C, G372C, K652E	R248C, S249C, G372C
PIK3CA	Mutations	Seborrheic keratosis: ~16% (103) Includes E542K, E545K, H1047R Epidermal nevi: ~27% (103) Includes E545G Fibroadipose hyperplasia: 90% (118) Includes H1047R and H1047L Hemimegalencephaly: E545K (119)	Melanoma: ~1%-3% (120,121) Includes E542K, E545K, H1047R Across cancers: 9%-18% (19,114,115,123) Includes E542K, E545K, E545G, H1047R	E542K, E545K, E545G, H1047R
ALK	Rearrangement	Inflammatory myofibroblastic tumor: ~50% (129) Includes TPM3-ALK, TPM4-ALK	Anaplastic large cell lymphoma: 60%-80% (130) Includes NPM-ALK, TPM3-ALK Adenocarcinoma of lung: 3%-7% (130) Includes EML4-ALK	TPM3-ALK
NOTCH 1	Mutations	Sun exposed skin: ~20% (176) Includes P168L, R353C, H486L, D464N, G394S, R176W, W1768*, P1770S, Q1923*	Cutaneous squamous cell carcinoma: ~75% (192) Includes R353C, C423F, Q610*, W1768*, P1770S, Q1923*	R353C, W1768*, P1770S, Q1923*
*TP53**	Mutations	Rheumatoid arthritis: 17-46% (137,138) Includes R177S, Q192L, R196*, K139R, H193Y, E224fs, N239S	One of the genes with highest mutation rate across tumors: ~40% (134,136) Includes H193Y, E224fs, N239S	H193Y, E224fs, N239S
*NF1**	Mutations	Neurofibromas and pilocytic astrocytomas (in setting of *NF1* germline mutations) (78)	Glioblastoma:15%-18% (156,157) Melanoma:13% (158) Adenocarcinoma of lung: 7% (159)	Associated with inactivating mutation or loss
NF2‡	Mutations	Schwannomas, meningioma, glioma and ependymoma astrocytomas (in setting of *NF2* germline mutations) (168)	Mesothelioma: 30%-50% (166) Hepatocellular carcinoma: 23% (166) Anaplastic thyroid carcinoma: 18% (166)	K44N, G197C, R200fs
HER2 protein	Overexpression	Ductal carcinoma in situ: ~27-56% (8,12,18)	Invasive breast cancer: ~11%-20% (85,86)	Not applicable

*Germline syndromes with increased cancer risk. ALK = anaplastic lymphoma receptor tyrosine kinase; BRAF = B-Raf proto-oncogene, serine/threonine; FGFR3 = fibroblast growth factor receptor 3; GNAQ = guanine nucleotide binding protein, q polypeptide; HER2 = human epidermal growth factor receptor 2; NF1 = neurofibromin 1; NF2 = neurofibromin 2; NRAS = neuroblastoma RAS viral oncogene homolog; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TP53 = tumor protein p53.
†Sturge Weber is because of GNAQ mutations that appear as a result of a postzygotic mutation, and hence patients have somatic mosaicism—the mutation is found in some but not all body cells.
‡Germline syndromes without increased cancer risk.

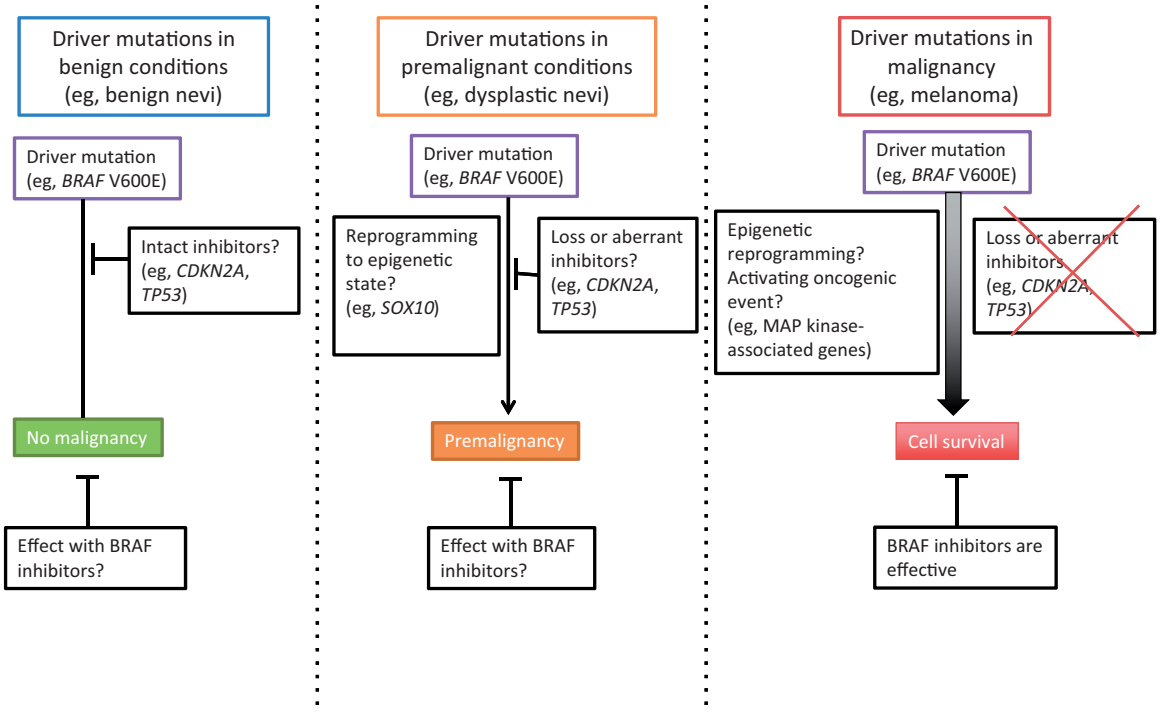

Figure 1. Driver mutations in benign, premalignant, and malignant diseases. Because BRAF inhibitors are effective in malignancies (such as melanoma) with *BRAF* mutations and do not cause routine regression of benign nevi, it is possible that development of melanoma is associated with loss of an inhibitor and/or an additional cofactor. However, it is not entirely clear which inhibitory or activating oncogenic cofactors are involved in carcinogenesis.

REVIEW

Another phenomenon of interest in unraveling some of these questions is the intriguing observation that stably transducing the "oncogene" *BRAF* V600E into melanocytes leads to blockage of cellular proliferation and to an increase in cellular senescence, despite phosphorylation of the downstream effector ERK (51). This finding contrasts with the transforming effect of *BRAF* V600E when introduced into p16-null melanocytes (p16 being one of two tumor suppressor gene products of CDKN2A) (50). This phenomenon has been designated "oncogene-induced senescence" (reviewed elsewhere [52–56]). The presence of insulin-like growth factor binding protein 7 (IGFBP7) was initially considered to be involved in *BRAF* V600E-mediated oncogene-induced senescence in melanocytic nevi and melanoma (57), but this observation has not been validated (51,58). A genome-wide investigation of differentially expressed genes in *BRAF* V600E melanocytic nevi compared with melanocytic nevi with *BRAF* wild-type revealed consistent upregulation of *CDKN2A*, *CDKN1C*, and *MITF* (59). Each of these is an intriguing candidate for maintaining the senescent state, but 20 distinct pathways were noted to be differentially expressed in this analysis and a functional dissection of these pathways has not been performed (59). Unbiased, genome-wide shRNA library screening for genes capable of reversing *BRAF* V600E-induced senescence identified *PTEN* as the most potent, and pharmacologic inhibition of PI3K signaling restored $p15^{INK4B}$-dependent senescence (49). The same group identified seven genes that, when silenced, could revert *BRAF*-associated senescence (60). However, only *RAS and RASEF* were differentially expressed in melanocytic nevi vs melanoma. Functional studies suggested that *RASEF* acts in a Rb-dependent fashion and affects expression of the senescence-associated secretome (60).

It remains puzzling that *BRAF* mutations are less commonly seen in melanoma than in melanocytic or dysplastic nevi. Recent descriptive and functional analysis suggest that alterations of *CDKN2A/B*, *PTEN*, *CDK4*, *CCND1*, *ERBB4*, and *AKT*, known to occur in human melanomas with high frequency, facilitate relief of oncogene-induced senescence, leading to selection of these melanocytic nevi during malignant evolution (15,16,61). However, the cooperation of these aforementioned alterations with *BRAF* V600E to hyperactive the MAP kinase pathway has not been established. Working out this mechanistic connection is essential to defining the most rational preventive strategy to explore in preclinical models and, eventually, in clinical trials. It remains possible that direct BRAF inhibition would be effective as a strategy to impede the ability of a cofactor to generate constitutive MAP kinase pathway signaling. Understanding the entire pathway that ties these phenomena together will provide other candidate points of intervention that could be more amenable to safe and effective use in the prevention setting.

RAS

RAS in Cancer

Three *RAS* genes (*KRAS*, *NRAS*, and *HRAS*) are amongst the most frequently altered oncogenes identified in human cancers. Mutations in these genes activate several downsteam pathways, depending on the mutation type and subtype (62–64).

The frequency of aberrations in each *RAS* gene differs depending on the underlying malignancy. *KRAS* (notably G12 and G13 mutations) is commonly mutated in patients with diverse malignancies such as pancreatic ductal adenocarcinoma (71%-98% of

cases), colorectal adenocarcinoma (35%-45%), and lung adenocarcinoma (19%-31%) (19,62,64). *NRAS* (notably Q61) aberrations have been associated with several tumors including melanoma (18%-28%), multiple myeloma (20%), and thyroid carcinoma (9%) (19,62,64). *HRAS* (G12, G13 and Q61) mutations are not as frequent when compared with *KRAS* or *NRAS* mutations; however, they have been reported in various cancer types including bladder urothelial carcinoma (1%-6%), head and neck squamous cell carcinoma (5%), and thyroid carcinoma (4%) (62,64). *RAS* mutations confer resistance to EGFR inhibitors in advanced colorectal and non–small cell lung cancers (65,66). To date, there are no effective therapies to directly overcome *RAS* mutations although multiple studies are ongoing, including application of agents targeting signals downstream of RAS (eg, MEK), screening compounds for synthetic lethality, identifying drugs that effectively interfere with RAS membrane localization, and the development of direct RAS inhibitors (62).

RAS in Premalignancy

For certain cancers, oncogenic *RAS* drives early neoplastic development and progression. Examples include progression of pancreatic premalignancy (intraepithelial neoplasia) driven by *KRAS* mutation, followed by inactivation of tumor suppressor genes *CDKN2A* and finally the inactivation of *TP53* and deletion of *SMAD4* (67,68). Similarly, the development of the colorectal adenoma-cancer neoplastic sequence is also attributed to a stepwise accumulation of mutations identified in premalignant adenomas, including those in the *APC*, *KRAS*, and *TP53* genes (69,70).

RAS in Benign Conditions

Although *NRAS* mutations are not as frequent when compared with the example of *BRAF* mutations (found in the majority of melanocytic nevi), the *NRAS* Q61K mutation is discerned in 6% to 14% of benign melanocytic nevi (71,72). Considering that the presence of *NRAS* mutation in melanoma is somewhat higher (18%-28%) (62,64) than in melanocytic nevi, it is speculated that *NRAS* mutations are one of the driver mutations for melanoma development. Interestingly, *NRAS* mutations (Q61K or Q61R) are detected in 70% to 95% of cases of congenital melanocytic nevi (benign melanocytic proliferation that develops in utero), which have a 465-fold increase risk of developing melanoma (73–75). *NRAS* mutation alone was not a strong driver for melanoma development in a melanoma mouse model, suggesting that additional mutations, eg, loss of *CKDN2A*, are required (76). The higher melanoma risk observed in patients with congenital melanocytic nevi suggests that length of time that *NRAS* mutations are harbored may be a factor in susceptibility to cancer development.

RAS Germline Mutations

Congenital *RAS* mutations are associated with RASopathies, which are a group of genetic developmental disorders affected by increased RAS-MAPK signaling. Although full detail of RASopathies is beyond the scope of this review and has been extensively described elsewhere (77–80), some of the syndromes associated with germline mutations in this pathway include Noonan syndrome (*PTPN11* and *KRAS* mutations), LEOPARD syndrome (*PTPN11* and *RAF1* mutations), neurofibromatosis type 1 (*NF1* mutation), Costello syndrome (*HRAS* mutation), and cardio-facio-cutaneous syndrome (*BRAF*, *MAP2K1* and *2*, *KRAS* mutations). Each RASopathy has unique clinical presentations; however, because of the common underlying mechanisms with increased RAS-MAPK signaling, they share overlapping characteristics with nonmalignant conditions such as craniofacial dysmorphology, cardiac malformation, cutaneous and musculoskeletal abnormalities, and neurocognitive impairment.

Importantly, patients with RASopathy do have an increased risk of malignancy, ranging from 1.6% to 15%, which manifests during early childhood and adolescence (77,81,82). Malignancies associated with RASopathies differ from syndrome to syndrome with some overlap. Neurofibromatosis 1 has been associated with malignant peripheral nerve sheath tumors (MPNSTs), pheochromocytomas, rhabdomyosarcomas, and gastrointestinal stromal tumors (GISTs) (78); Costello syndrome, with an increased risk of rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma (77); and Noonan syndrome, with acute lymphoblastic leukemia, neuroblastoma, and rhabdomyosarcoma (82).

GNAQ

GNAQ-activating mutations lead to an increase in MAP kinase pathway signals. Interestingly, they are found in about 88% of Sturge-Weber syndrome (*GNAQ* R183Q). This syndrome is characterized by specific clinical features such as port-wine stains affecting the skin, as well as leptomeningeal vascular malformations. An increased risk of malignancy has not been documented (83).

Mutations in *GNAQ* are also found in patients with cancer. For instance, *GNAQ* alterations are frequent in uveal melanoma, with a minority (3%-6%) harboring R183Q, while *GNAQ* Q209L is detected in 22% to 45% of patients (84) (Table 1).

The reason that Sturge-Weber patients do not develop cancer may be because the *GNAQ* mutations they harbor develop as a consequence of somatic mosaicism and, hence, are not found in all body cells. (Somatic mosaicism occurs as a result of a post-zygotic mutation and refers to the occurrence of two genetically distinct populations of cells within an individual. In contrast to classic inherited mutations, somatic mosaic alterations may affect only a portion of the body and are not transmitted to children.) Hence, mutations in *GNAQ* may require specific tissue contexts to produce cancer.

HER2

HER2 in Invasive Breast Cancer vs Ductal Carcinoma In Situ

HER2 can be overexpressed, amplified, or, less commonly, mutated in a variety of cancers (85,86). Treatment with anti-HER2 agents is US Food and Drug Administration (FDA)–approved for breast and gastric cancers and has activity in other malignancies as well (87).

Ductal carcinoma in situ (DCIS) is the most common type of premalignant noninvasive breast cancer (88). Although HER2 overexpression is implicated in the pathogenesis of breast cancer (89–91), HER2 is more commonly overexpressed in patients with DCIS (~27%-56%) (8,12,18) when compared with invasive breast cancer (~11%-20%) (85,86) (Table 1). The underlying reason why HER2, which is considered to be an important driver of breast cancer (91), is more highly expressed in noninvasive disease, is unclear. Recent clinical trial data illustrate the

complexity of HER2 status in DCIS and invasive breast cancer and suggest that ERBB2 status in DCIS can be both prognostic and predictive. Increased ERBB2 mRNA expression correlated with risk of ipsilateral DCIS but not invasive breast cancer. Radiation therapy was more effective in HER2 overexpressing DCIS, both in reducing ipsilateral DCIS and invasive breast cancer (92). However, there is no clinical data on the efficacy of HER2-targeted therapy by HER2 expression status in DCIS.

FGFR3

FGFR3 in Cancer

Fibroblast growth factor receptor 3 (FGFR3) belongs to a family of tyrosine kinase receptors, and its oncogenic role has been proposed as a mechanism underlying the development and progression of cancer (93). *FGFR3* aberrations are found in multiple tumor types, most commonly being described in urothelial bladder cancer and some reports in cervical cancer (94–99). Aberrations include *FGFR3* R248C, S249C, and G372C in cancer (94–99) (Table 1). These mutations result in the FGFR3 kinase enzyme becoming locked in the activated position, leading to ligand-independent signaling activation (97,98,100). However, the frequency of *FGFR3* mutations in bladder cancer paradoxically decreases with advanced and higher-grade tumors (frequency of *FGFR3* mutations in TaG1 tumor: ~61%, TaG2: ~58%, TaG3: ~34%, T1G3: ~17%, T2-T4, high-grade tumors: ~11%) (94,101). Although similar literature for cervical cancer in this regard is lacking, it requires further investigation.

FGFR3 in Benign Conditions

FGFR3-activating mutations have been reported in 18% to 85% of seborrheic keratoses; these are benign lesions with no risk of cancer (102–105) (Table 1). The wide range of frequency of *FGFR3* mutations may be because of different patient characteristics, locations of the seborrheic keratoses that were biopsied (seborrheic keratoses from head and neck had a higher frequency of *FGFR3* mutations when compared with the ones from the trunk and extremities (102)), and experimental designs. Similarly, 33% of epidermal nevi harbor *FGFR3* R248C mutation (106). Some of the specific *FGFR3* mutations, including R248C, S249C, and G372C alterations, are also found in urothelial bladder and cervical cancers while others are not (Table 1) (94–97,99). Functional studies of *FGFR3* mutations in benign skin conditions are limited. Hafner et al. (107) evaluated keratinocyte cell lines transduced with either *FGFR3* wild-type or the R248C mutation and showed that *FGFR3*-mutant keratinocytes had lower levels of apoptosis and enhanced phosphorylation of ERK1/2 when compared with wild-type controls. However, in the same in vitro model, *FGFR3* mutations did not alter migration and senescence when compared with wild-type keratinocytes. Furthermore, in clinical samples of seborrheic keratosis, there were no differences in Ki-67 expression between wild-type and *FGFR3*-mutant samples, suggesting that FGFR3 may not contribute to proliferation in seborrheic keratosis (102,107).

FGFR3 Germline Mutations

FGFR3 germline mutations have an inhibitory impact on bone growth that leads to dwarfism syndromes, with mutations identical to those discerned in some cancers and seborrheic keratoses (eg, R248C and S249C) (108–110). FGFR3 inhibitor exposure restored dwarf mice harboring *FGFR3* mutations to a normal phenotype (111). Although patients with dwarfism syndromes have decreased life expectancy (average 10 years shorter), mainly because of heart disease–related mortality (112), these patients have no documented increased incidence of cancer or of seborrheic keratoses.

PIK3CA

Mutations in *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha* (*PIK3CA*) are found in diverse malignancies (113). Tumors harboring *PIK3CA* mutations may respond to PI3K/Akt/mTOR inhibitors (19,114,115), confirming the *PIK3CA* oncogenic role. *PIK3CA* mutations are also detected in a subset of benign epidermal nevi and seborrheic keratoses (103) (Table 1).

PIK3CA in Cancer

PIK3CA is part of the PI3K signaling pathway that is crucial for cell growth and survival (116). Certain *PIK3CA* anomalies, including E542K, E545K, and H1047R mutations, have been found in multiple cancer types including colon, breast, and bladder cancer (113). It has been reported that *PIK3CA* mutations predict response to treatment with combination regimens that include a PI3K/AKT/mammalian target of rapamycin (mTOR) inhibitor (19,114,115). Further relevance of PIK3CA as a therapeutic target has recently been gleaned from phase I/II trials with PI3K alpha selective inhibitors. Three such agents produce highly comparable results. Notably, these trials also demonstrated that the response rate with these agents as monotherapy is lower than that observed with BRAF, EGFR, and ALK inhibitors in their respective genotype-defined populations in melanoma and non–small cell lung cancer. Furthermore, emergence of clones that are wild-type for PIK3CA in progressing tumors (117) highlights the variable role of PIK3CA across cancers. Taken together, the data suggests that targeting PIK3CA alone may be less useful than in combination regimens, consistent with the presence of codrivers in tumors with abnormalities in this gene.

PIK3CA in Benign and Premalignant Conditions

Similar to the *FGFR3* and *BRAF* mutation story, *PIK3CA*-activating alterations are implicated in the pathogenesis of seborrheic keratosis (~16%) and epidermal nevi (~27%), with mutations identical to those found in certain malignancies (includes E542K, E545K, and H1047R) (103). *PIK3CA*-activating alterations are also reported in patients with fibroadipose hyperplasia, which is a syndrome of nonmalignant progressive segmental overgrowth of fibrous and adipose tissue, where 90% of patients were found to have either *PIK3CA* H1047R or H1047L mutations (118), and in hemimegalencephaly (HME), characterized by nonmalignant overgrowth of either one of the two cerebral hemispheres, as well as other brain malformations (119). Although *PIK3CA* mutations are uncommon in melanoma (~1%-3%) (120,121) or basal cell and squamous cell carcinoma of skin (122), they are found in 9% to 18% of other solid tumors (19,114,115,123) (Table 1). In the context of the PI3K/Akt/mTOR pathway, *AKT1*-activating mutations, which are found in diverse malignancies (124), are also reported in seborrheic keratoses (E17K: 2%) (125). Lastly, the PI3K/Akt/mTOR pathway, an

important driver in lung premalignacy, could be reversed by an inhibitor of this pathway (126).

ALK

Fusion of *ALK* with different genomic partners leads constitutively to activation and drives tumorigenesis (127). The ALK inhibitors crizotinib and ceritinib are very effective and have been FDA-approved in lung adenocarcinoma with *ALK* rearrangement (35). Interestingly, *ALK* rearrangement is also reported in patients with benign inflammatory myofibroblastic tumors (128,129) (Table 1).

ALK in Cancer

ALK rearrangement has been described in a variety of tumors, including anaplastic large cell lymphoma (NPM-ALK: 60%-80%, TPM3-ALK: 12%-18%), lung adenocarcinoma (EML4-ALK: 3%-7%), and breast cancer (EML4-ALK: 0%-2.4%) (130). ALK inhibitors have successfully prosecuted ALK-altered tumors (35,131,132).

ALK in Benign Tumors

Interestingly, about half of inflammatory myofibroblastic tumors harbor rearrangements in the ALK locus (TPM3 or TPM4-ALK), leading to aberrant ALK signaling (129). Inflammatory myofibroblastic tumors (also called inflammatory pseudotumors) occur in different anatomic locations including lung, liver, breast, soft tissue, and colon (133). Although locally destructive forms of this disease have been reported, metastases are uncommon, with a less than 5% risk (133). Therapies include resection or observation, and, if necessary, chemotherapy and radiation have been used (133). ALK inhibition with crizotinib has been evaluated and shown to have clinical benefit (128).

TP53

The *TP53* tumor suppressor gene is amongst the most frequently mutated in cancer, being reported in 40% to 50% of human malignancies (134–136). Despite the strong association between *TP53* abnormalities and malignancy, mutations in this gene have also been described in benign diseases as below (137,138) (Table 1).

TP53 Mutations in Cancer

TP53 mutations can result in both gain of function and loss of function; the latter is mostly associated with a dominant-negative effect over wild-type p53 (139). Mutations are especially frequent in serous ovarian (95% of patients) and serous endometrial carcinomas (89%) (134). Furthermore, patients with germline *TP53* mutations have Li-Fraumeni syndrome that is associated with a high incidence of cancer (140).

TP53 Mutations in Synovium of Rheumatoid Arthritis

Rheumatoid arthritis is linked to synovial tissue hyperplasia but is not reported to be a direct risk for cancer development. It has been documented that 17% to 46% (137,138) of synovial tissues from patients with rheumatoid arthritis had alterations in *TP53* that are identical to the mutations seen in malignancies (eg, H193Y, E224fs, N239S); these mutations were not observed in patients with osteoarthritis (138). Even so, Reme et al. (137) followed four patients with *TP53*-mutated rheumatoid arthritis for two years and none developed signs of malignancy. Further, synovial sarcoma is not a complication of rheumatoid arthritis. These data indicate that the oncogenic role of mutated *TP53* is tissue-context dependent.

Although the role of *TP53* mutation in the pathogenesis of rheumatoid arthritis remains to be fully clarified, in vitro and in vivo work shows that inactivation of *TP53* in synovial cells leads to stimulation of metalloproteinase and cytokines, which are in turn associated with enhanced proliferation and invasiveness of synoviocytes (141). Further, Angelo and colleagues (142) reported that mutated *TP53* leads to interleukin-6 (IL-6) overexpression, at least in part by modulating specific transcription factor binding to the IL-6 promoter. These observations are of special interest because IL-6 is a potent proinflammatory agent that plays a critical role in the pathogenesis of inflammatory disease and is important for both joint destruction and systemic manifestations of rheumatoid arthritis (143). Furthermore, tocilizumab, which binds the IL-6 receptor, is FDA-approved for treatment of active, moderate to severe rheumatoid arthritis (and systemic juvenile idiopathic arthritis) (144).

TP53 Germline Mutations

Mutations in germline *TP53* are associated with the Li-Fraumeni syndrome, a rare disorder that greatly increases the risk of developing several types of cancer (breast cancer, sarcomas, brain tumors, leukemias, and adrenocortical carcinomas), particularly in children and young adults (140).

CDKN2A

CDKN2A in Cancer

Aberrations in cyclin-dependent kinase (CDK) pathways disrupt cell cycle restriction and contribute to genomic instability and tumor proliferation (145,146). Cyclin D1 forms complex with CDK4/6, leading to Rb protein phosphorylation and subsequent G1 cell-cycle progression mediated by E2F transcription factor. This pathway is regulated by inhibitors including CDKN2A (p16) and/or CDKN2B (p15) (147). Loss or inactivating mutations of CDKN2A can lead to alteration in CDK pathway and tumorigenesis. Aberrations in CDKN2A (mostly loss or hypermethylation) have been observed in about 19% of patients with diverse malignancies and have been associated with poor clinical outcome (148,149).

CDKN2A in Premalignant Conditions

Aberration in *CDKN2A* is observed in multiple premalignant conditions, including pancreatic intraepithelial neoplasia (42%) (17), colorectal adenomas (34%) (10), and Barrett's esophagus (33%) (9). However, Shain et al. recently reported that aberration of *CDKN2A* was a late event in melanoma development, exclusively observed in patients with invasive melanoma and not associated with precursor skin lesions that were commonly associated with *BRAF* or *HRAS* aberrations (16). The latter observations suggest that *CDKN2A* aberrations are critical for melanoma development (Figure 1).

CDKN2A Germline Mutations

CDKN2A germline mutations are associated with familial atypical multiple mole melanoma (FAMMM) syndrome, which is an autosomal dominant condition characterized by high numbers of dysplastic nevi (>50) and a history of melanoma in one or more first- or second-degree relatives (150,151). *CDKN2A* germline mutations increase the risk of melanoma (152,153) and pancreatic cancer (154), and possibly sarcoma, breast, and esophageal cancers (155).

NF1

NF1 in Cancer

Neurofibromin 1 (*NF1*) is a tumor suppressor gene that encodes RAS GTPase-activating protein (GAP) (78). *NF1*-inactivating mutations or loss lead to hyperactivation of RAS and increase downstream effector signaling such as that by PI3K/Akt/mTOR and MAP kinase (62).

Somatic mutations of *NF1* (inactivating mutations or loss) are identified in a variety of sporadic cancers, including glioblastoma (15%-18%) (156,157), melanoma (~13%) (158), and lung adenocarcinoma (~7%) (159). *NF1* mutations are considered to be mutually exclusive with *NRAS* or *BRAF* mutations, suggesting their dedicated role in the RAS-MAPK pathway (78,158). Preclinical studies suggest that *NF1* mutations are potentially targetable with mTOR inhibitors such as everolimus (160) or MEK inhibitors such as trametinib (161), or by combining both mTOR and MEK inhibitors, and that suppression of signals downstream of RAS with MEK and/or mTOR is capable of controlling tumorigenesis (162,163).

NF1 Germline Mutations

Neurofibromatosis type 1, an autosomal dominant disorder caused by *NF1*-inactivating mutations (164), can include cutaneous, neurologic, optic, and orthopedic abnormalities and benign and malignant tumors (78,164). Many tumors associated with neurofibromatosis type 1 originate from the neural crest cell (pheochromocytomas, neurofibromas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors) but can also be derived from neuroepithelial cells (pilocytic astrocytomas); there are also non-neural crest-derived tumors such as rhabdomyosarcoma and gastrointestingal stromal tumors (78).

Neurofibromatosis type 1–associated cancers can demonstrate various degrees of aggressiveness, even though they may arise from the same cell types. For example, in considering lesions that derive from the neural crest cell, cutaneous neurofibroma are typically benign and do not transform; plexiform neurofibroma can invade adjacent tissue but remain nonmetastatic while malignant peripheral nerve sheath tumors are highly aggressive with strong metastatic potential (78). To date, it is not entirely understood why different degrees of aggressiveness can develop in tumors of similar origin in patients with neurofibromatosis type 1. Mouse models with neurofibroma and malignant peripheral nerve sheath tumors showed both conditions had sustained ERK activation (165), suggesting that other molecular factors may be responsible for cancer aggressiveness. Identifying such factors may lead to better therapeutic targeting for patients with neurofibromatosis type 1 and sporadic cancers.

NF2

NF2 in Cancer

The *Neurofibromin 2* (*NF2*) gene is a tumor suppressor that encodes a protein known as merlin, which affects diverse cell signaling pathways (166,167). Notably, merlin inhibits mTORC1 and the complex formation of Src/FAK, thus controlling PI3K and RAS-MAPK signaling pathways, respectively (166,167). Thus, inactivating mutations of *NF2* lead to increases in PI3K and RAS-MAPK signaling.

Somatic mutations in *NF2* genes have been found in diverse cancer types, including mesothelioma (30%-50%), hepatocellular carcinoma (~23%), and anaplastic thyroid carcinoma (~18%) (166). These malignancies are, however, not increased in patients with germline *NF2* mutations. Not surprisingly, somatic mutations in the *NF2* gene are also identified in some sporadic tumors that are associated with neurofibromatosis type 2, including schwannoma (42%), meningioma (31%), glioma (27%), and ependymoma (4%) (166).

NF2 Germline Mutations

Neurofibromatosis type 2, an autosomal dominant disorder (168), is characterized by the development of benign tumors including schwannomas (notably vestibular schwannomas), meningioma, and low-grade central nervous system neoplasms (glioma and ependymoma) (168). As mentioned, some sporadic cases of these neoplasms harbor somatic *NF2* mutations (166). However, to date, there is no data that suggests that patients with neurofibromatosis type 2 are predisposed to an increased risk of malignancies (166,168). This observation is perplexing. It has been postulated that the lack of a vulnerability to an increased incidence of malignant tumors in individuals with neurofibromatosis type 2 could be because of the type of mutations found in the germline vs the somatic settings. Indeed, germline alterations in *NF2* are more likely to be nonsense or frameshift mutations (166,169) while missense mutations are more frequently found in sporadic cancers when compared with patients with neurofibromatosis type 2 (166,169). However, this explanation is not complete because there is overlap between the germline *NF2* mutations and those found in *NF2*-bearing sporadic cancers (166,169). Further investigation is required to understand the mechanisms of *NF2* mutations and tumorigenesis, which may lead to the identification of novel approaches targeting *NF2* in both patients with neurofibromatosis type 2 and in sporadic cancers with this mutation. Interestingly, Subbiah et al. (170) reported a patient with neurofibromatosis type 2 and multiple neoplasms (meningioma, ependymoma and schwannomas) that showed regression when treated with an mTOR inhibitor-containing regimen (and it is known that *NF2* mutations activate the mTOR pathway). Trials using targeted therapies in patients with neurofibromatosis type 2 are ongoing.

Implications for Prevention Strategies

Despite the genetic driver complexities in premalignancy, the first precision medicine prevention trial was reported recently in high-risk (presence of genetic driver) oral premalignancy (171), beginning a new era of molecular selection trial designs in cancer prevention (172). Remarkable progress in genome-wide sequencing, big-data analytics, liquid-biopsy technologies, and

deep understanding of the inflammatory tumor microenvironment are decoding the molecular and cellular factors that influence the development of cancer, transforming cancer prevention (173).

Of interest in this regard, activating *EGFR* mutations, present in about 20% of lung adenocarcinoma (and associated with dramatic responses to EGFR inhibitors), have been reported to be a very early genetic driver in the development of this subset of lung cancer, detected in 43% of histologically normal epithelium surrounding (within and adjacent to) *EGFR*-mutant lung cancer (174). No mutation was seen in normal lung tissues when lung adenocarcinoma did not harbor *EGFR* mutation. Preclinical models with mice carrying doxycycline-inducible, lung-specific, mutant *EGFR* transgenes (L858R or L747–S752 deletion mutation) showed that the EGFR mutation is sufficient for lung cancer development and necessary for tumor maintenance (withdrawal of doxycycline led to tumor regression) (175).

Also of relevance to prevention, ultra-deep sequencing of 74 cancer genes in 234 biopsies of sun-exposed eyelid epidermis revealed two to six mutations per megabase per cell, similar to that seen in many malignancies (176). The most common mutations were in the *NOTCH1/2* and *FAT1* genes. *NOTCH1* driver mutations have also been detected in oral premalignancy (177). *Cyclin D1* amplification was one of the first genetic drivers identified in upper aerodigestive tract with severe dysplasia, and Izzo et al. showed that targeting cyclin D1 with retinoid-induced ubiquitinization (proteolysis) reduced genomic instability and cancer rates (178). Data from lung squamous cell carcinoma and recently in lung squamous premalignancy identified 3q26.33-3q29 (including SOX2) amplification/overexpression as a genetic driver in this setting (179). Prevention strategies in high-risk lesions targeting genetic drivers (eg, dysplastic nevi in FAMMM, PI3K pathway in lung dysplasia, HER2 in DCIS) are underway or being planned (as described earlier in this paper).

Recently, driver mutations including *BRAF* have been detected in circulating cell-free DNA (obtained from blood samples designated liquid biopsies) in patients with lung premalignancy (atypical adenomatous hyperplasia [AAH]) (180). Similarly, in patients with congenital melanocytic nevi, circulating cell-free, DNA-derived *BRAF* V600E mutations and circulating nevus cells were detected (181). The extent to which such observations might complicate the application of liquid biopsies for prevention or early detection of melanoma or other malignancies, and any potential application of BRAF inhibitors in prevention, remains to be determined.

Although the focus of this paper is on solid tumors, somatic and germline driver mutations have also been well described in some hematologic disorders (eg, germline *ETV6* mutations in familial thrombocytopenia and diverse hematologic malignancies (182); and somatic *JAK2* mutations in myeloproliferative disorders (183)). In some cases, genetic drivers of blood cancers were detected from whole-exome sequencing of DNA in peripheral blood cells from apparently healthy adults and were associated with future blood cancer risk (184). On the other hand, *BCR-ABL* transcripts ($P210^{BCR-ABL}$), a hallmark of chronic myelogenous leukemia (CML; but not generally $p190^{BCR-ABL}$) (185,186), are found in the blood of healthy individuals in about 10% to 30% of cases (187–189). Despite this fact, monitoring *BCR-ABL* transcript levels has been successfully utilized to assess the treatment response from tyrosine kinase inhibitors in patients with CML (190).

Overall, these observations indicate that classic genomic oncogenic drivers can be found in premalignancy and in normal individuals. In some cases, their presence foretells a predisposition to malignancy while in others it may not. The key to successful prevention strategies will therefore be a deep interrogation of the implications of genomic drivers in different contexts (191).

Conclusions

All of the genomic alterations (eg, *BRAF*, *K-, N-, and H-RAS*, *GNAQ*, *EGFR*, *HER2*, *FGFR3*, *PIK3CA*, *ALK*, *TP53*, *CDKN2A*, *NF1*, and *NF2*) discussed herein have been associated with tumor development and implicated as driver alterations (22,89,93,116,135). However, these driver alterations are also variably found in benign and premalignant conditions, occasionally at even higher frequencies than in their malignant counterparts (Table 1). Many of these abnormalities can also be germline. In some cases, they predispose to high rates of malignancy while in other cases they do not.

Overall, several important observations emerge. First, despite classic theories of clonal selection of driver alterations in the progression from benign lesions to premalignancy to malignancy, there appear to be important exceptions. These include *BRAF* V600E mutations, which are paradoxically more common in benign melanocytic nevi (~80% mutation rate) than in dysplastic nevi (~60%) or melanoma (~40%-45%) (13,22–25,37,38); HER2, which is more frequently overexpressed in patients with ductal carcinoma in situ (~27%-56% of cases) when compared with its malignant counterpart, invasive breast cancer (~11%-20%) (8,12,18,85,86); and *FGFR3* mutations, which decrease in frequency with grade of bladder cancer (low-grade tumors, ~61% of cases; high-grade, ~11%) (94,101) (Table 1). In each of these examples, the importance of the alterations to the tumor is beyond doubt, as demonstrated by responses to cognate therapies and other experimental evidence. The presence of these "drivers" at higher rates in benign or premalignant lesions and, in the case of benign melanocytic nevi, their frequent failure to regress with BRAF inhibitor therapy suggest that there is an endogenous inhibitor and/or one or more oncogenic cofactor alterations that are required for malignant evolution to occur (42,43,47,49,50,59,60).

A second observation that becomes apparent is that tissue context may be important in the propensity of a "driver" alteration to produce a cancer. For instance, *TP53* mutations are amongst the most common underlying tumor suppressor gene alterations across tumor types. Yet, they can also be found in the synovium of patients with rheumatoid arthritis and, in that tissue context, are not associated with malignancy (Table 1) (137,138). Similarly, identical *FGFR3*-activating mutations that are seen in solid tumors are also found in benign conditions, such as seborrheic keratoses, with no malignant potential (102–105).

A third pertinent observation relates to the presence of some of these driver aberrations in germline form. In some cases, such as Li-Fraumeni syndrome, whose hallmark is germline *TP53* mutations (140), affected individuals are clearly predisposed to a variety of malignancies. However, in other cases, such as dwarfism syndromes whose germline *FGFR3* alterations are identical to those found to be drivers in their somatic form, there is no documented increase in cancer in individuals harboring the germline abnormality (112). These findings suggest that the oncogenic potential of certain genomic drivers may also be developmental context–dependent, with early compensatory mechanisms perhaps moderating the oncogenic potential of the alteration.

In summary, the observation of presumed genomic drivers at high frequency in some benign and premalignant lesions, as well as in germline conditions without an increased incidence of cancer, suggests that the functional impact of a gene alteration may be context dependent, with the attendant genomic landscape as well as the tissue and developmental setting being germane. There are several clinically important questions that will need to be addressed. If certain genomic drivers are seen at similar (or greater) frequencies in benign conditions compared with malignant diseases, are we therapeutically targeting the right genetic driver? Are there underlying intact tumor suppressors in benign conditions that prevent driver mutations from promoting tumorigenesis? Can we reliably use genomic alterations as a screening tool for early detection of cancer or as a marker for prevention or treatment response such as with liquid biopsies? Finally, the role of certain driver mutations in tumor initiation and premalignancy, rather than progression and malignancy, merits exploration.

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REVIEW

References

1. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature*. 1998;396(6712):643–649.
2. Munoz J, Swanton C, Kurzrock R. Molecular profiling and the reclassification of cancer: divide and conquer. *Am Soc Clin Oncol Educ Book*. 2013;127–34.
3. Muller FL, Colla S, Aquilanti E, et al. Passenger deletions generate therapeutic vulnerabilities in cancer. *Nature*. 2012;488(7411):337–342.
4. Pleasance ED, Cheetham RK, Stephens PJ, et al. A comprehensive catalogue of somatic mutations from a human cancer genome. *Nature*. 2010;463(7278):191–196.
5. Greenman C, Stephens P, Smith R, et al. Patterns of somatic mutation in human cancer genomes. *Nature*. 2007;446(7132):153–158.
6. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature*. 2009;458(7239):719–724.
7. Scott KL, Nogueira C, Heffernan TP, et al. Proinvasion metastasis drivers in early-stage melanoma are oncogenes. *Cancer Cell*. 2011;20(1):92–103.
8. Allred DC, Clark GM, Molina R, et al. Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. *Hum Pathol*. 1992;23(9):974–979.
9. Bian YS, Osterheld MC, Fontolliet C, et al. p16 inactivation by methylation of the CDKN2A promoter occurs early during neoplastic progression in Barrett's esophagus. *Gastroenterology*. 2002;122(4):1113–1121.
10. Petko Z, Ghiassi M, Shuber A, et al. Aberrantly methylated CDKN2A, MGMT, and MLH1 in colon polyps and in fecal DNA from patients with colorectal polyps. *Clin Cancer Res*. 2005;11(3):1203–1209.
11. Taylor BS, Schultz N, Hieronymus H, et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell*. 2010;18(1):11–22.
12. Rakovitch E, Nofech-Mozes S, Hanna W, et al. HER2/neu and Ki-67 expression predict non-invasive recurrence following breast-conserving therapy for ductal carcinoma in situ. *Br J Cancer*. 2012;106(6):1160–1165.
13. Saroufim M, Novy M, Taraif S, et al. BRAF mutational epidemiology in dysplastic nevi: does different solar UV radiation exposure matter? *J Eur Acad Dermatol Venereol*. 2014;28(5):615–625.
14. Cancer Genome Atlas N. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015;517(7536):576–582.
15. McNeal AS, Liu K, Nakhate V, et al. CDKN2B Loss Promotes Progression from Benign Melanocytic Nevus to Melanoma. *Cancer Discov*. 2015;5(10):1072–1085.
16. Shain AH, Yeh I, Kovalyshyn I, et al. The Genetic Evolution of Melanoma from Precursor Lesions. *N Engl J Med*. 2015;373(20):1926–1936.
17. Tang B, Li Y, Qi G, et al. Clinicopathological Significance of CDKN2A Promoter Hypermethylation Frequency with Pancreatic Cancer. *Sci Rep*. 2015;5:13563.
18. Williams KE, Barnes NL, Cramer A, et al. Molecular Phenotypes of DCIS predict overall and invasive recurrence. *Ann Oncol*. 2015;26(5):1019–1025.
19. Tsimberidou AM, Iskander NG, Hong DS, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. *Clin Cancer Res*. 2012;18(22):6373–6383.
20. Smalley KS, Nathanson KL, Flaherty KT. Genetic subgrouping of melanoma reveals new opportunities for targeted therapy. *Cancer Res*. 2009;69(8):3241–3244.
21. Sullivan RJ, Flaherty K. MAP kinase signaling and inhibition in melanoma. *Oncogene*. 2013;32(19):2373–2379.
22. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949–954.
23. Mar VJ, Liu W, Devitt B, et al. The role of BRAF mutations in primary melanoma growth rate and survival. *Br J Dermatol*. 2015;173(1):76–82.
24. Meric-Bernstam F, Brusco L, Shaw K, et al. Feasibility of Large-Scale Genomic Testing to Facilitate Enrollment Onto Genomically Matched Clinical Trials. *J Clin Oncol*. 2015;33(25):2753–2762.
25. Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol*. 2011;29(10):1239–1246.
26. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507–2516.
27. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. *Lancet*. 2012;379(9829):1893–1901.
28. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380(9839):358–365.
29. Henary H, Hong DS, Falchook GS, et al. Melanoma patients in a phase I clinic: molecular aberrations, targeted therapy and outcomes. *Ann Oncol*. 2013;24(8):2158–2165.
30. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. *N Engl J Med*. 2015;373(8):726–736.
31. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med*. 2012;366(8):707–714.
32. Falchook GS, Lewis KD, Infante JR, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. *Lancet Oncol*. 2012;13(8):782–789.
33. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380–2388.
34. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239–246.
35. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;370(13):1189–1197.
36. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.
37. Kumar R, Angelini S, Snellman E, et al. BRAF mutations are common somatic events in melanocytic nevi. *J Invest Dermatol*. 2004;122(2):342–348.
38. Pollock PM, Harper UL, Hansen KS, et al. High frequency of BRAF mutations in nevi. *Nat Genet*. 2003;33(1):19–20.
39. Yeh I, von Deimling A, Bastian BC. Clonal BRAF mutations in melanocytic nevi and initiating role of BRAF in melanocytic neoplasia. *J Natl Cancer Inst*. 2013;105(12):917–919.
40. Tsao H, Bevona C, Goggins W, et al. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. *Arch Dermatol*. 2003;139(3):282–288.
41. Tiersten AD, Grin CM, Kopf AW, et al. Prospective follow-up for malignant melanoma in patients with atypical-mole (dysplastic-nevus) syndrome. *J Dermatol Surg Oncol*. 1991;17(1):44–48.
42. Haenssle HA, Kraus SL, Brehmer F, et al. Dynamic changes in nevi of a patient with melanoma treated with vemurafenib: importance of sequential dermoscopy. *Arch Dermatol*. 2012;148(10):1183–1185.
43. Cohen PR, Bedikian AY, Kim KB. Appearance of New Vemurafenib-associated Melanocytic Nevi on Normal-appearing Skin: Case Series and a Review of Changing or New Pigmented Lesions in Patients with Metastatic Malignant Melanoma After Initiating Treatment with Vemurafenib. *J Clin Aesthet Dermatol*. 2013;6(5):27–37.
44. Su F, Viros A, Milagre C, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. *N Engl J Med*. 2012;366(3):207–215.

45. Zimmer L, Hillen U, Livingstone E, et al. Atypical melanocytic proliferations and new primary melanomas in patients with advanced melanoma undergoing selective BRAF inhibition. *J Clin Oncol*. 2012;30(19):2375–2383.
46. Venesio T, Chiorino G, Balsamo A, et al. In melanocytic lesions the fraction of BRAF V600E alleles is associated with sun exposure but unrelated to ERK phosphorylation. *Mod Pathol*. 2008;21(6):716–726.
47. Patton EE, Widlund HR, Kutok JL, et al. BRAF mutations are sufficient to promote nevi formation and cooperate with p53 in the genesis of melanoma. *Curr Biol*. 2005;15(3):249–254.
48. Kaufman CK, Mosimann C, Fan ZP, et al. A zebrafish melanoma model reveals emergence of neural crest identity during melanoma initiation. *Science*. 2016;351(6272):aad2197.
49. Vredeveld LC, Possik PA, Smit MA, et al. Abrogation of BRAFV600E-induced senescence by PI3K pathway activation contributes to melanomagenesis. *Genes Dev*. 2012;26(10):1055–1069.
50. Gray-Schopfer VC, Cheong SC, Chong H, et al. Cellular senescence in naevi and immortalisation in melanoma: a role for p16? *Br J Cancer*. 2006;95(4):496–505.
51. Scurr LL, Pupo GM, Becker TM, et al. IGFBP7 is not required for B-RAF-induced melanocyte senescence. *Cell*. 2010;141(4):717–727.
52. Prieur A, Peeper DS. Cellular senescence in vivo: a barrier to tumorigenesis. *Curr Opin Cell Biol*. 2008;20(2):150–155.
53. Courtois-Cox S, Jones SL, Cichowski K. Many roads lead to oncogene-induced senescence. *Oncogene*. 2008;27(20):2801–2809.
54. Campisi J. Cellular senescence: putting the paradoxes in perspective. *Curr Opin Genet Dev*. 2011;21(1):107–112.
55. Campisi J. Cellular senescence as a tumor-suppressor mechanism. *Trends Cell Biol*. 2001;11(11):S27–S31.
56. Bennett DC. Genetics of melanoma progression: the rise and fall of cell senescence. *Pigment Cell Melanoma Res*. 2015; in press.
57. Wajapeyee N, Serra RW, Zhu X, et al. Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7. *Cell*. 2008;132(3):363–374.
58. Schrama D, Kneitz H, Willmes C, et al. Lack of correlation between IGFBP7 expression and BRAF mutational status in melanoma. *J Invest Dermatol*. 2010;130(3):897–898.
59. Bloethner S, Snellman E, Bermejo JL, et al. Differential gene expression in melanocytic nevi with the V600E BRAF mutation. *Genes Chromosomes Cancer*. 2007;46(11):1019–1027.
60. Kaplon J, Homig-Holzel C, Gao L, et al. Near-genomewide RNAi screening for regulators of BRAF(V600E) -induced senescence identifies RASEF, a gene epigenetically silenced in melanoma. *Pigment Cell Melanoma Res*. 2014;27(4):640–652.
61. Flaherty KT, Hodi FS, Fisher DE. From genes to drugs: targeted strategies for melanoma. *Nat Rev Cancer*. 2012;12(5):349–361.
62. Cox AD, Fesik SW, Kimmelman AC, et al. Drugging the undruggable RAS: Mission possible? *Nat Rev Drug Discov*. 2014;13(11):828–851.
63. Ihle NT, Byers LA, Kim ES, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst*. 2012;104(3):228–239.
64. Stephen AG, Esposito D, Bagni RK, et al. Dragging ras back in the ring. *Cancer Cell*. 2014;25(3):272–281.
65. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol*. 2005;23(25):5900–5909.
66. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med*. 2008;359(17):1757–1765.
67. Bryant KL, Mancias JD, Kimmelman AC, et al. KRAS: feeding pancreatic cancer proliferation. *Trends Biochem Sci*. 2014;39(2):91–100.
68. Hidalgo M. Pancreatic cancer. *N Engl J Med*. 2010;362(17):1605–1617.
69. Hadac JN, Leystra AA, Paul Olson TJ, et al. Colon Tumors with the Simultaneous Induction of Driver Mutations in APC, KRAS, and PIK3CA Still Progress through the Adenoma-to-carcinoma Sequence. *Cancer Prev Res (Phila)*. 2015;8(10):952–961.
70. Smith G, Carey FA, Beattie J, et al. Mutations in APC, Kirsten-ras, and p53-alternative genetic pathways to colorectal cancer. *Proc Natl Acad Sci U S A*. 2002;99(14):9433–9438.
71. Poynter JN, Elder JT, Fullen DR, et al. BRAF and NRAS mutations in melanoma and melanocytic nevi. *Melanoma Res*. 2006;16(4):267–273.
72. Tschandl P, Berghoff AS, Preusser M, et al. NRAS and BRAF mutations in melanoma-associated nevi and uninvolved nevi. *PLoS One*. 2013;8(7):e69639.
73. Bauer J, Curtin JA, Pinkel D, et al. Congenital melanocytic nevi frequently harbor NRAS mutations but no BRAF mutations. *J Invest Dermatol*. 2007;127(1):179–182.
74. Charbel C, Fontaine RH, Malouf GG, et al. NRAS mutation is the sole recurrent somatic mutation in large congenital melanocytic nevi. *J Invest Dermatol*. 2014;134(4):1067–1074.
75. Krengel S, Hauschild A, Schafer T. Melanoma risk in congenital melanocytic naevi: a systematic review. *Br J Dermatol*. 2006;155(1):1–8.
76. Ackermann J, Frutschi M, Kaloulis K, et al. Metastasizing melanoma formation caused by expression of activated N-RasQ61K on an INK4a-deficient background. *Cancer Res*. 2005;65(10):4005–4011.
77. Gripp KW, Lin AE. Costello syndrome: a Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from HRAS germline mutations. *Genet Med*. 2012;14(3):285–292.
78. Ratner N, Miller SJ. A RASopathy gene commonly mutated in cancer: the neurofibromatosis type 1 tumour suppressor. *Nat Rev Cancer*. 2015;15(5):290–301.
79. Rauen KA. The RASopathies. *Annu Rev Genomics Hum Genet*. 2013;14:355–369.
80. Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr Opin Genet Dev*. 2009;19(3):230–236.
81. Kratz CP, Franke L, Peters H, et al. Cancer spectrum and frequency among children with Noonan, Costello, and cardio-facio-cutaneous syndromes. *Br J Cancer*. 2015;112(8):1392–1397.
82. Kratz CP, Rapisuwon S, Reed H, et al. Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes. *Am J Med Genet C Semin Med Genet*. 2011;157C(2):83–89.
83. Shirley MD, Tang H, Gallione CJ, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. *N Engl J Med*. 2013;368(21):1971–1979.
84. Van Raamsdonk CD, Griewank KG, Crosby MB, et al. Mutations in GNA11 in uveal melanoma. *N Engl J Med*. 2010;363(23):2191–2199.
85. Yan M, Parker BA, Schwab R, et al. HER2 aberrations in cancer: implications for therapy. *Cancer Treat Rev*. 2014;40(6):770–780.
86. Yan M, Schwaederle M, Arguello D, et al. HER2 expression status in diverse cancers: review of results from 37,992 patients. *Cancer Metastasis Rev*. 2015;34(1):157–164.
87. Falchook GS, Janku F, Tsao AS, et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. *J Thorac Oncol*. 2013;8(2):e19–e20.
88. Virnig BA, Tuttle TM, Shamliyan T, et al. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst*. 2010;102(3):170–178.
89. Guy CT, Webster MA, Schaller M, et al. Expression of the neu protooncogene in the mammary epithelium of transgenic mice induces metastatic disease. *Proc Natl Acad Sci U S A*. 1992;89(22):10578–10582.
90. Hudziak RM, Schlessinger J, Ullrich A. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. *Proc Natl Acad Sci U S A*. 1987;84(20):7159–7163.
91. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*. 1987;235(4785):177–182.
92. Thorat M, Wagner S, Jones LJ, et al. Prognostic and predictive relevance of HER2 status in ductal carcinoma in situ: Results from the UK/ANZ DCIS trial. *San Antonio Breast Cancer Symposium (December)*. 2015;P3-07-02.
93. Shaw AT, Hsu PP, Awad MM, et al. Tyrosine kinase gene rearrangements in epithelial malignancies. *Nat Rev Cancer*. 2013;13(11):772–787.
94. Cancer Genome Atlas Research N. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014;507(7492):315–322.
95. Cappellen D, De Oliveira C, Ricol D, et al. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nat Genet*. 1999;23(1):18–20.
96. Helsten T, Elkin S, Arthur E, et al. The FGFR Landscape in Cancer: Analysis of 4853 Tumors by Next Generation Sequencing. *Clin Cancer Res*. 2016;22(1):259–267.
97. Helsten T, Schwaederle M, Kurzrock R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. *Cancer Metastasis Rev*. 2015;34(3):479–496.
98. Parish A, Schwaederle M, Daniels G, et al. Fibroblast Growth Factor Family Aberrations in Cancers: Clinical and Molecular Characteristics. *Cell Cycle*. 2015;14(13):2121–2128.
99. Wu R, Connolly D, Ngelangel C, et al. Somatic mutations of fibroblast growth factor receptor 3 (FGFR3) are uncommon in carcinomas of the uterine cervix. *Oncogene*. 2000;19(48):5543–5546.
100. Ahmad I, Iwata T, Leung HY. Mechanisms of FGFR-mediated carcinogenesis. *Biochim Biophys Acta*. 2012;1823(4):850–860.
101. Hernandez S, Lopez-Knowles E, Lloreta J, et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. *J Clin Oncol*. 2006;24(22):3664–3671.
102. Hafner C, Hartmann A, van Oers JM, et al. FGFR3 mutations in seborrheic keratoses are already present in flat lesions and associated with age and localization. *Mod Pathol*. 2007;20(8):895–903.
103. Hafner C, Lopez-Knowles E, Luis NM, et al. Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. *Proc Natl Acad Sci U S A*. 2007;104(33):13450–13454.
104. Hafner C, van Oers JM, Hartmann A, et al. High frequency of FGFR3 mutations in adenoid seborrheic keratoses. *J Invest Dermatol*. 2006;126(11):2404–2407.
105. Hida Y, Kubo Y, Arase S. Activation of fibroblast growth factor receptor 3 and oncogene-induced senescence in skin tumours. *Br J Dermatol*. 2009;160(6):1258–1263.

106. Hafner C, van Oers JM, Vogt T, et al. Mosaicism of activating FGFR3 mutations in human skin causes epidermal nevi. *J Clin Invest*. 2006;116(8):2201–2207.
107. Hafner C, Di Martino E, Pitt E, et al. FGFR3 mutation affects cell growth, apoptosis and attachment in keratinocytes. *Exp Cell Res*. 2010;316(12):2008–2016.
108. Tavormina PL, Shiang R, Thompson LM, et al. Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. *Nat Genet*. 1995;9(3):321–328.
109. Rousseau F, el Ghouzzi V, Delezoide AL, et al. Missense FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD1). *Hum Mol Genet*. 1996;5(4):509–512.
110. van Rhijn BW, van Tilborg AA, Lurkin I, et al. Novel fibroblast growth factor receptor 3 (FGFR3) mutations in bladder cancer previously identified in non-lethal skeletal disorders. *Eur J Hum Genet*. 2002;10(12):819–824.
111. Jonquoy A, Mugniery E, Benoist-Lasselin C, et al. A novel tyrosine kinase inhibitor restores chondrocyte differentiation and promotes bone growth in a gain-of-function Fgfr3 mouse model. *Hum Mol Genet*. 2012;21(4):841–851.
112. Wynn J, King TM, Gambello MJ, et al. Mortality in achondroplasia study: a 42-year follow-up. *Am J Med Genet A*. 2007;143A(21):2502–2511.
113. Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. *Br J Cancer*. 2006;94(4):455–459.
114. Janku F, Hong DS, Fu S, et al. Assessing PIK3CA and PTEN in early-phase trials with PI3K/AKT/mTOR inhibitors. *Cell Rep*. 2014;6(2):377–387.
115. Janku F, Wheler JJ, Westin SN, et al. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. *J Clin Oncol*. 2012;30(8):777–782.
116. Hennessy BT, Smith DL, Ram PT, et al. Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nat Rev Drug Discov*. 2005;4(12):988–1004.
117. Dupont Jensen J, Laenkholm AV, Knoop A, et al. PIK3CA mutations may be discordant between primary and corresponding metastatic disease in breast cancer. *Clin Cancer Res*. 2011;17(4):667–677.
118. Lindhurst MJ, Parker VE, Payne F, et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. *Nat Genet*. 2012;44(8):928–933.
119. Lee JH, Huynh M, Silhavy JL, et al. De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. *Nat Genet*. 2012;44(8):941–945.
120. Curtin JA, Stark MS, Pinkel D, et al. PI3-kinase subunits are infrequent somatic targets in melanoma. *J Invest Dermatol*. 2006;126(7):1660–1663.
121. Omholt K, Krockel D, Ringborg U, et al. Mutations of PIK3CA are rare in cutaneous melanoma. *Melanoma Res*. 2006;16(2):197–200.
122. Hafner C, Landthaler M, Vogt T. Activation of the PI3K/AKT signalling pathway in non-melanoma skin cancer is not mediated by oncogenic PIK3CA and AKT1 hotspot mutations. *Exp Dermatol*. 2010;19(8):e222–227.
123. Bendell JC, Rodon J, Burris HA, et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. *J Clin Oncol*. 2012;30(3):282–290.
124. Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*. 2007;448(7152):439–444.
125. Hafner C, Toll A, Fernandez-Casado A, et al. Multiple oncogenic mutations and clonal relationship in spatially distinct benign human epidermal tumors. *Proc Natl Acad Sci U S A*. 2010;107(48):20780–20785.
126. Gustafson AM, Soldi R, Anderlind C, et al. Airway PI3K pathway activation is an early and reversible event in lung cancer development. *Sci Transl Med*. 2010;2(26):26ra25.
127. Hallberg B, Palmer RH. Mechanistic insight into ALK receptor tyrosine kinase in human cancer biology. *Nat Rev Cancer*. 2013;13(10):685–700.
128. Butrynski JE, D'Adamo DR, Hornick JL, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med*. 2010;363(18):1727–1733.
129. Lawrence B, Perez-Atayde A, Hibbard MK, et al. TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. *Am J Pathol*. 2000;157(2):377–384.
130. Grande E, Bolos MV, Arriola E. Targeting oncogenic ALK: a promising strategy for cancer treatment. *Mol Cancer Ther*. 2011;10(4):569–579.
131. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378.
132. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013;368(25):2385–2394.
133. Kovach SJ, Fischer AC, Katzman PJ, et al. Inflammatory myofibroblastic tumors. *J Surg Oncol*. 2006;94(5):385–391.
134. Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. *Nature*. 2013;502(7471):333–339.
135. Muller PA, Vousden KH. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell*. 2014;25(3):304–317.
136. Said R, Hong DS, Warneke CL, et al. P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy. *Oncotarget*. 2013;4(5):705–714.
137. Reme T, Travaglio A, Gueydon E, et al. Mutations of the p53 tumour suppressor gene in erosive rheumatoid synovial tissue. *Clin Exp Immunol*. 1998;111(2):353–358.
138. Firestein GS, Echeverri F, Yeo M, et al. Somatic mutations in the p53 tumor suppressor gene in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A*. 1997;94(20):10895–10900.
139. Petitjean A, Mathe E, Kato S, et al. Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database. *Hum Mutat*. 2007;28(6):622–629.
140. Olivier M, Goldgar DE, Sodha N, et al. Li-Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. *Cancer Res*. 2003;63(20):6643–6650.
141. Sun Y, Cheung HS. p53, proto-oncogene and rheumatoid arthritis. *Semin Arthritis Rheum*. 2002;31(5):299–310.
142. Angelo LS, Talpaz M, Kurzrock R. Autocrine interleukin-6 production in renal cell carcinoma: evidence for the involvement of p53. *Cancer Res*. 2002;62(3):932–940.
143. Hashizume M, Mihara M. The roles of interleukin-6 in the pathogenesis of rheumatoid arthritis. *Arthritis*. 2011;2011:765624.
144. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis*. 2008;67(11):1516–1523.
145. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674.
146. Malumbres M, Barbacid M. Cell cycle, CDKs and cancer: a changing paradigm. *Nat Rev Cancer*. 2009;9(3):153–166.
147. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol*. 2006;24(11):1770–1783.
148. Kato S, Schwaederle M, Daniels GA, et al. Cyclin-dependent kinase pathway aberrations in diverse malignancies: clinical and molecular characteristics. *Cell Cycle*. 2015;14(8):1252–1259.
149. Schwaederle M, Daniels GA, Piccioni DE, et al. Next generation sequencing demonstrates association between tumor suppressor gene aberrations and poor outcome in patients with cancer. *Cell Cycle*. 2015;14(11):1730–1737.
150. Eckerle Mize D, Bishop M, Resse E, et al. Familial Atypical Multiple Mole Melanoma Syndrome. In:DL, Riegert-Johnson LA, BoardmanT, Hefferon et al., eds. *Cancer Syndromes*. Bethesda, MD; 2009.
151. Goldstein AM, Chan M, Harland M, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. *J Med Genet*. 2007;44(2):99–106.
152. Harland M, Cust AE, Badenas C, et al. Prevalence and predictors of germline CDKN2A mutations for melanoma cases from Australia, Spain and the United Kingdom. *Hered Cancer Clin Pract*. 2014;12(1):20.
153. Puntervoll HE, Yang XR, Vetti HH, et al. Melanoma prone families with CDK4 germline mutation: phenotypic profile and associations with MC1R variants. *J Med Genet*. 2013;50(4):264–270.
154. Bartsch DK, Sina-Frey M, Lang S, et al. CDKN2A germline mutations in familial pancreatic cancer. *Ann Surg*. 2002;236(6):730–737.
155. Lynch HT, Brand RE, Hogg D, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. *Cancer*. 2002;94(1):84–96.
156. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321(5897):1807–1812.
157. Verhaak RG, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010;17(1):98–110.
158. Krauthammer M, Kong Y, Bacchiocchi A, et al. Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas. *Nat Genet*. 2015;47(9):996–1002.
159. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. 2008;455(7216):1069–1075.
160. Endo M, Yamamoto H, Setsu N, et al. Prognostic significance of AKT/mTOR and MAPK pathways and antitumor effect of mTOR inhibitor in NF1-related and sporadic malignant peripheral nerve sheath tumors. *Clin Cancer Res*. 2013;19(2):450–461.
161. Nissan MH, Pratilas CA, Jones AM, et al. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. *Cancer Res*. 2014;74(8):2340–2350.
162. Malone CF, Fromm JA, Maertens O, et al. Defining key signaling nodes and therapeutic biomarkers in NF1-mutant cancers. *Cancer Discov*. 2014;4(9):1062–1073.
163. Watson AL, Anderson LK, Greeley AD, et al. Co-targeting the MAPK and PI3K/AKT/mTOR pathways in two genetically engineered mouse models of schwann cell tumors reduces tumor grade and multiplicity. *Oncotarget*. 2014;5(6):1502–1514.
164. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol*. 2009;61(1):1–14; quiz 15-16.
165. Jessen WJ, Miller SJ, Jousma E, et al. MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. *J Clin Invest*. 2013;123(1):340–347.
166. Schroeder RD, Angelo LS, Kurzrock R. NF2/merlin in hereditary neurofibromatosis 2 versus cancer: biologic mechanisms and clinical associations. *Oncotarget*. 2014;5(1):67–77.

167. Xiao GH, Gallagher R, Shetler J, et al. The NF2 tumor suppressor gene product, merlin, inhibits cell proliferation and cell cycle progression by repressing cyclin D1 expression. *Mol Cell Biol*. 2005;25(6):2384–2394.
168. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. *Orphanet J Rare Dis*. 2009;4:16.
169. Ahronowitz I, Xin W, Kiely R, et al. Mutational spectrum of the NF2 gene: a meta-analysis of 12 years of research and diagnostic laboratory findings. *Hum Mutat*. 2007;28(1):1–12.
170. Subbiah V, Slopis J, Hong DS, et al. Treatment of patients with advanced neurofibromatosis type 2 with novel molecularly targeted therapies: from bench to bedside. *J Clin Oncol*. 2012;30(5):e64–e68.
171. William WN Jr, Papadimitrakopoulou V, Lee JJ, et al. Erlotinib and the Risk of Oral Cancer: The Erlotinib Prevention of Oral Cancer (EPOC) Randomized Clinical Trial. *JAMA Oncol*. 2015;2(2):209–216.
172. Bauman JE, Grandis J. Oral Cancer Chemoprevention-The End of EPOC, the Beginning of an Epoch of Molecular Selection. *JAMA Oncol*. 2015;2(2):178–179.
173. Kensler TW, Spira A, Garber JE, et al. Transforming Cancer Prevention through Precision Medicine and Immune-oncology. *Cancer Prev Res (Phila)*. 2016;9(1):2–10.
174. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res*. 2005;65(17):7568–7572.
175. Politi K, Zakowski MF, Fan PD, et al. Lung adenocarcinomas induced in mice by mutant EGF receptors found in human lung cancers respond to a tyrosine kinase inhibitor or to down-regulation of the receptors. *Genes Dev*. 2006;20(11):1496–1510.
176. Martincorena I, Roshan A, Gerstung M, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. *Science*. 2015;348(6237):880–886.
177. Izumchenko E, Sun K, Jones S, et al. Notch1 mutations are drivers of oral tumorigenesis. *Cancer Prev Res (Phila)*. 2015;8(4):277–286.
178. Izzo JG, Papadimitrakopoulou VA, Liu DD, et al. Cyclin D1 genotype, response to biochemoprevention, and progression rate to upper aerodigestive tract cancer. *J Natl Cancer Inst*. 2003;95(3):198–205.
179. Ooi AT, Gower AC, Zhang KX, et al. Molecular profiling of premalignant lesions in lung squamous cell carcinomas identifies mechanisms involved in stepwise carcinogenesis. *Cancer Prev Res (Phila)*. 2014;7(5):487–495.
180. Izumchenko E, Chang X, Brait M, et al. Targeted sequencing reveals clonal genetic changes in the progression of early lung neoplasms and paired circulating DNA. *Nat Commun*. 2015;6:8258.
181. De Giorgi V, Pinzani P, Salvianti F, et al. Circulating benign nevus cells detected by ISET technique: warning for melanoma molecular diagnosis. *Arch Dermatol*. 2010;146(10):1120–1124.
182. Zhang MY, Churpek JE, Keel SB, et al. Germline ETV6 mutations in familial thrombocytopenia and hematologic malignancy. *Nat Genet*. 2015;47(2):180–185.
183. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365(9464):1054–1061.
184. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477–2487.
185. Kurzrock R, Shtalrid M, Romero P, et al. A novel c-abl protein product in Philadelphia-positive acute lymphoblastic leukaemia. *Nature*. 1987;325(6105):631–635.
186. Kurzrock R, Gutterman JU, Talpaz M. The molecular genetics of Philadelphia chromosome-positive leukemias. *N Engl J Med*. 1988;319(15):990–998.
187. Biernaux C, Loos M, Sels A, et al. Detection of major bcr-abl gene expression at a very low level in blood cells of some healthy individuals. *Blood*. 1995;86(8):3118–3122.
188. Bose S, Deininger M, Gora-Tybor J, et al. The presence of typical and atypical BCR-ABL fusion genes in leukocytes of normal individuals: biologic significance and implications for the assessment of minimal residual disease. *Blood*. 1998;92(9):3362–3367.
189. Ismail SI, Naffa RG, Yousef AM, et al. Incidence of bcrabl fusion transcripts in healthy individuals. *Mol Med Rep*. 2014;9(4):1271–1276.
190. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013;122(6):872–884.
191. Campbell JD, Mazzilli SA, Reid ME, et al. The Case for a Pre-Cancer Genome Atlas (PCGA). *Cancer Prev Res*. 2016;9(2):119–124.
192. Wang NJ, Sanborn Z, Arnett KL, et al. Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. *Proc Natl Acad Sci U S A*. 2011;108(43):17761–17766.