

REVIEW ARTICLE

LRIG and cancer prognosis

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ABSTRACT

Background. Optimal treatment decisions for cancer patients require reliable prognostic and predictive information. However, this information is inadequate in many cases. Several recent studies suggest that the leucine-rich repeats and immunoglobulin-like domains (LRIG) genes, transcripts, and proteins have prognostic implications in various cancer types.

Material and methods. Relevant literature was identified on PubMed using the key words *lrig1*, *lrig2*, and *lrig3*. *LRIG* mRNA expression in cancer versus normal tissues was investigated using the OncoPrint database.

Results. The three human LRIG genes, *LRIG1*, *LRIG2*, and *LRIG3*, encode single-pass transmembrane proteins. *LRIG1* is a negative regulator of growth factor signaling that has been shown to function as a tumor suppressor in vitro and in vivo in mice. The functions of *LRIG2* and *LRIG3* are less well defined. LRIG gene and protein expression are commonly dysregulated in human cancer. In early stage breast cancer, *LRIG1* copy number was recently shown to predict early and late relapse in addition to overall survival; in nasopharyngeal carcinoma, loss of *LRIG1* is also associated with poor survival. LRIG gene and protein expression have prognostic value in breast cancer, uterine cervical cancer, head-and-neck cancer, glioma, non-small cell lung cancer, prostate cancer, and cutaneous squamous cell carcinoma. In general, expression of *LRIG1* and *LRIG3* is associated with good survival, whereas expression of *LRIG2* is associated with poor survival. Additionally, *LRIG1* regulates cellular sensitivity to anti-cancer drugs, which indicates a possible role as a predictive marker.

Conclusions. LRIG gene statuses and mRNA and protein expression are clinically relevant prognostic indicators in several types of human cancer. We propose that LRIG analyses could become important when making informed and individualized clinical decisions regarding the management of cancer patients.

The need for new and better prognostic and predictive markers in clinical oncology is urgent because of the obvious over- and under-treatment of patients occurring today. One major explanation for suboptimal treatment decisions is the lack of prognostic and predictive markers that can be used to accurately predict disease recurrence and therapy response. The emerging tumor suppressor leucine-rich repeats and immunoglobulin-like domains- (LRIG-) 1 and its paralogs *LRIG2* and *LRIG3*, have prognostic value in diverse types of cancer, including breast cancer [1,2], uterine cervical cancer [3–5], head-and-neck cancer [6–8], glioma [9,10], prostate cancer [11], and cutaneous squamous cell carcinoma [12]. A brief mini-review on LRIG in cancer was recently

published [13]; however, no thorough overview of the clinical implications of the many new and important findings in the LRIG field have been presented since our previous LRIG review in 2007 [14]. Here, we summarize the current knowledge on LRIG and cancer prognosis and discuss the potential future role of LRIG genes and proteins as clinically useful molecular markers in human cancer.

Material and methods

Literature survey

PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) was searched using the search terms *lrig1*, *lrig2*, and *lrig3*, which yielded 109, 25, and 29 entries,

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respectively, of which 107 were non-redundant, peer-reviewed original articles written in the English language. Of these articles, 17 contained both LRIG expression data and patient survival data, and 11 presented significant up- or down-regulation of LRIG1 mRNA or protein in cancer tissue compared with normal tissue; all of these articles were included in the present review. Additionally, key papers describing the identification and molecular, developmental, and physiological functions of the LRIG proteins were included.

Analysis of LRIG mRNA expression in different cancer types

The possible differences in *LRIG* mRNA expression in cancer versus normal tissues was investigated using the OncoPrint database (Compendia Bioscience, Ann Arbor, MI, USA) with OncoPrint 4.4.3 Research Edition with the following settings: threshold (p-value), 10^{-4} ; threshold (fold change), all; threshold (gene rank), all. For each cancer type, changes in expression were reported as over- or under-expression if they were found in two or more data sets.

Results

The LRIG family

The human *LRIG* gene family comprises three genes, *LRIG1*, *LRIG2*, and *LRIG3*, which are located at chromosomes 3p14, 1p13.1, and 12q14.1, respectively [15–17]. The encoded trans-membrane proteins share a similar structure with an extra-cellular or luminal leucine-rich-repeat domain and three immunoglobulin-like domains, a transmembrane domain, and a cytosolic domain. All three LRIG genes and proteins are widely expressed in human and mouse tissues [15–20]. The subcellular localization of LRIG proteins varies and includes the plasma membrane, cytoplasm, perinuclear region, and nucleus [14]. However, in certain pathological tissues, such as psoriatic skin, the subcellular distributions of the LRIG proteins are altered [21].

LRIG1 is an emerging tumor suppressor

More than 10 years ago, *LRIG1* was hypothesized to be a tumor suppressor gene [15,22]. Experimental and clinical data have subsequently supported this original hypothesis. Accumulating evidence shows that LRIG1 suppresses the proliferation of normal and transformed cells. Cells whose proliferation is inhibited by LRIG1 include human embryonic kidney cells [23], prostate cancer cells [11,24], mouse fibroblasts [24], keratinocytes [25], bladder

cancer cells [26], breast cancer cells [1,27,28], astrocytoma and glioblastoma cells [29,30], African green monkey kidney cells [30], nasopharyngeal carcinoma cells [7], and lung cancer cells [31]. At the molecular level, LRIG1 negatively regulates growth factor signaling mediated by several oncogenic receptor tyrosine kinases. This appears to be achieved through different mechanisms: LRIG1 induces the ubiquitylation and degradation of the epidermal growth factor receptor (EGFR) family members EGFR, ERBB2 (also called HER2), ERBB3, and ERBB4 [23,24], destabilizes the MET receptor [27,32], and physically interacts with the RET receptor to inhibit RET phosphorylation and downstream signaling [33]. The platelet-derived growth factor (PDGF) receptor PDGFR α is down-regulated by LRIG1 through an as-yet undefined mechanism [34]. Furthermore, LRIG1 also appears to be able to regulate cytokine and bone morphogenetic protein (BMP) signaling; *Lrig1*-deficient cells show an increased responsiveness to interleukin-6 [35], and SMA-10/LRIG mutant nematodes show impaired BMP signaling [36]. In addition to the cell-autonomous functions, LRIG1 ectodomains can be shed to negatively regulate EGFR signaling in a paracrine manner [30,37]. Thus, several mechanisms for the LRIG1 protein that negatively regulates receptor signaling have been described thus far, and the non-cell-autonomous inhibition of growth factor receptor signaling via soluble LRIG1 ectodomains could be a mechanism that could be exploited for anti-cancer treatment [30,37,38]. Recently, *Lrig1* was proven to function as a tumor suppressor in mice. *Lrig1*-deficient mice show hyperproliferation of epidermal [25,39,40] and intestinal [41,42] stem cells, airway hyperplasia [31], and development of spontaneous intestinal adenomas [42].

The role of LRIG2 and LRIG3 in cancer

LRIG2 and LRIG3 are less studied than LRIG1. Recently, it was found that a subgroup of individuals with urofacial syndrome carries mutations in *LRIG2* [43]. *Lrig2*-deficient mice display transiently reduced growth and increased spontaneous mortality [34]. Intriguingly and in contrast with LRIG1, LRIG2 may promote gliomagenesis, as *Lrig2*-deficient mice are protected against PDGF-induced glioma [34]. This finding is consistent with results showing that the down-regulation of LRIG2 in a human glioma cell line results in decreased cell proliferation and increased apoptosis [44]. *Lrig3*-deficient mice show disturbed development of the inner ear and present with craniofacial defects [45,46]. In the amphibian *Xenopus laevis*, LRIG3 inhibits fibroblast growth factor (FGF) signaling [47]. Recently, mammalian

LRIG3 was proposed to oppose the function of LRIG1, thus stabilizing the EGFR family proteins [48]. Despite these intriguing observations, the roles of LRIG2 and LRIG3 in human cancer remain poorly understood.

LRIG expression is dysregulated in human cancer

All of the LRIG genes and proteins are expressed in most, if not all, normal human tissues [15–18]. However, relatively little is known about the regulation of LRIG expression. The transcription of *LRIG1* can be induced using growth factors [23] or steroid hormones [1,11]. In ERBB2-positive cancer cell lines, over-expression of ERBB2 down-regulates the estrogen receptor, thereby suppressing the estrogen-induced transcription of *LRIG1* [1,28]. The natural compound gambogic acid up-regulates LRIG1 in glioma cells through the activation of AMP-regulated kinase, thereby inhibiting the proliferation of these cells [49]. In the lung, LRIG1 appears to be down-regulated by smoking [50], which is consistent with the observation that in early stage uterine cervical tumors, LRIG1 levels are lower in smoking women than in non-smoking women [3]. The transcription of *LRIG2* has been demonstrated to be regulated by the concomitant expression of the transcription factors *FOS*, *TAF1*, and *YY1* [51]. This could potentially be relevant in cancer biology because *FOS* is a well-established proto-oncogene. Expression of *Lrig3* is regulated by *Netrin* during mouse embryonic inner ear lateral canal development [45]; however, the significance of the regulation of *LRIG3* in other organs and in neoplasia is unknown.

Given that the LRIG proteins are important regulators of growth factor signaling and cell proliferation, it is not surprising that their expression is often dysregulated in human cancer. For example, it was recently demonstrated that down-regulation of LRIG1 is associated with the benign-to-malignant transformation of ocular-surface squamous tumors [52]. Additionally, LRIG1 mRNA and protein have been reported to be significantly down-regulated in neoplastic tissue compared with the corresponding normal tissue in breast cancer and ERBB2-positive breast cancer [28], clear cell renal cell carcinoma [53], chronic lymphocytic leukemia [54], oral squamous cell carcinoma [55], astrocytoma [56], lung squamous cell carcinoma and carcinoma in situ [31,50], nasopharyngeal squamous cell carcinoma [7], and colorectal cancer [13]. However, LRIG1 mRNA and protein are significantly over-expressed in prostate cancer [11] and breast cancer of the luminal A subtype [13], which are two cancer types that are largely driven by steroid hormones. An

analysis of the gene expression data sets at Oncomine confirmed that *LRIG* genes are aberrantly expressed in many neoplastic tissues compared with their normal tissue counterparts. In particular, dysregulated *LRIG* expression was found in cancers of the bladder, breast, uterine cervix, colorectum, head-and-neck, hematopoietic system, ovary, and prostate and also in glioma (Figure 1). Notably, this list derived from Oncomine likely displays only a fraction of all of the cancer types with dysregulated LRIG expression because stringent criteria for over- and under-expression were used in the analysis (see Material and methods). The biological interpretation of dysregulated LRIG expression in cancer tissues is, however, complicated by the fact that expression is physiologically regulated and may be selected for (or against) during tumor evolution [11]. That is, it cannot be a priori deduced whether a given LRIG gene or protein will be over- or under-expressed in a certain cancer type at a specific time point. Additionally, genomic aberrations of *LRIG* genes are frequently found. In nasopharyngeal carcinoma, *LRIG1* is commonly deleted [6], and in breast cancer, *LRIG1* shows both increased and decreased gene copy numbers, and gene recombination events have been suggested [2,57,58].

LRIG as prognostic indicators in human cancer

Loss of LRIG1 predicts early and late relapse in breast cancer. Late relapse in breast cancer remains an important clinical problem. Currently, there are very few, if any, molecular markers that robustly predict the risk of late relapse in early stage breast cancer.

CANCER TYPE	LRIG1	LRIG2	LRIG3
Bladder	Green		
Oligodendroglioma	Red		
Glioblastoma		Red	
Breast	Green	Green	Green
Cervical SCC	Green		
Colorectal	Green, Red		Green
Head and neck	Green		
AML	Green		
T-ALL	Green		
NSCLC	Green	Green	Red
Lymphoma	Green	Green	Red
Ovarian	Red	Red	
Prostate	Red		

Figure 1. Over- and under-expression of LRIG genes in human cancers compared with their normal tissue counterparts. Altered expression is indicated only when two or more studies in the Oncomine database showed over- or under-expression for their respective cancer type. Red indicates over-expression and green indicates under-expression in tumors versus normal tissue. Colorectal cancer showed both over- and under-expression of LRIG1. AML, acute myeloid leukemia; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; T-ALL, T-cell acute lymphoblastic leukemia.

A recent study of gene copy number variation in 971 stage I/II breast tumors revealed that loss of the *LRIG1* locus is an independent risk factor for early and late relapse and for death [2]. In another recent study, *LRIG1* expression was higher in patients with tumors expressing the estrogen receptor, and data collected from Oncomine showed that high expression of *LRIG1* in estrogen receptor-positive and lymph node-negative breast cancer was correlated with prolonged relapse-free survival [1]. Given that *LRIG1* negatively regulates the ERBB2 receptor and the proliferation of ERBB2-positive breast cancer cells, it will be interesting to investigate whether *LRIG1* also has prognostic value in ERBB2-positive breast cancer. In any case, if the *LRIG1* copy number or expression level is confirmed to predict late relapse in early stage breast cancer, *LRIG1* could become a clinically relevant molecular classifier in breast cancer.

In uterine cervical cancer, expression of LRIG1 and LRIG2 is associated with good and poor prognosis, respectively. *LRIG* expression was studied via immunohistochemistry in 128 women with uterine cervical cancer [3,4] and 86 women with uterine adenocarcinoma [5]. In cervical squamous cell carcinoma, both *LRIG1* and *LRIG2* were independent prognostic factors. Intriguingly, in early stage squamous cell carcinoma, high expression of *LRIG1* correlated with good survival [3], whereas high expression of *LRIG2* correlated with poor survival [4]. When low expression of *LRIG1* and high expression of *LRIG2* were combined, a subgroup of patients with a very poor prognosis was identified [4], which suggests that *LRIG1* and *LRIG2* could be useful prognostic markers in early stage uterine squamous cell carcinoma; it also suggests that *LRIG1* and *LRIG2* could have different and opposing functions in which *LRIG1* suppresses cancer and *LRIG2* promotes cancer. No correlation between *LRIG* expression and survival was found in cervical squamous cell carcinoma at later stages [3]. In uterine cervical adenocarcinoma, expression of both *LRIG1* and *LRIG3* correlated with good survival [5]. When all the significant parameters, *LRIG1*, *LRIG3*, HPV status, age, histology, and FIGO stage were included in a multivariate analysis, only *LRIG3* and age showed independent statistical significance [5]. In summary, these studies indicate that *LRIG* proteins could be relevant prognostic markers in cervical cancers of different histologies and for patients of different stages.

Head-and-neck cancer. In nasopharyngeal carcinoma, the *LRIG1* locus is frequently deleted and the mRNA levels decreased [6]. In a panel of 48 clinical samples,

30% showed a loss of *LRIG1*, and concomitant loss of *LRIG1* and *ADAMTS9* was associated with a poor clinical outcome. More recently, an immunohistochemical analysis of 44 metastatic nasopharyngeal carcinomas revealed a significant correlation between low *LRIG1* expression and poor outcome [7]. Similarly, in oropharyngeal carcinoma, an immunohistochemical study of 278 cases showed that *LRIG1* was an independent positive prognostic factor [8]. Of note, the subgroup of patients with oropharyngeal tumors that were human papilloma virus-positive and expressed high *LRIG1* levels showed a very favorable prognosis. These criteria may possibly define a subgroup of patients where adjuvant treatment is not necessary, whereas patients with *LRIG1*-negative tumors could comprise a subgroup that could benefit from intensified treatment. Together, these studies indicate that *LRIG1* could be a clinically useful prognostic marker in head-and-neck cancer.

Perinuclear expression of LRIG proteins is associated with prolonged survival in astrocytic tumors. The prognostic impact of the expression of *LRIG* proteins was investigated by immunohistochemistry in 404 patients with astrocytic brain tumors [9]. Perinuclear immunoreactivity of all *LRIG* proteins was inversely correlated with World Health Organization (WHO) grade, which is a known prognostic factor in astrocytic tumors. Additionally, perinuclear and cytoplasmic staining of *LRIG3* was correlated with a lower proliferation index, and perinuclear staining and WHO tumor grade were independent prognostic factors in the analyzed cohort. Regrettably, the currently established prognostic and predictive molecular markers in glioma, *MGMT* promoter methylation, chromosome 1p and 19q co-deletion, and *IDH1* mutations were not analyzed in this patient series, thereby precluding a comparison between *LRIG3* and these markers. Nevertheless, the data suggest that the expression of the *LRIG* proteins and in particular perinuclear expression of *LRIG3* could be important when evaluating the prognosis of astrocytic tumors.

Expression of LRIG2 predicts poor survival in oligodendroglial tumors. In an immunohistochemical study including 63 patients with oligodendroglial brain tumors, *LRIG* expression was assessed in relation to various clinical parameters and patient survival [10]. Similar to the situation in early stage cervical squamous cell carcinoma, *LRIG2* was an independent prognostic factor in oligodendroglial tumors. Unfortunately, neither in this glioma series were *MGMT* promoter methylation status, chromosome 1p and 19q co-deletion, nor *IDH1* mutations ana-

lyzed. However, a subgroup analysis suggested that there was no association between LRIG2 expression and the numerical status of chromosome 1p. The finding that LRIG2 expression was associated with poor oligodendroglioma patient survival was further corroborated in an experimental study showing a correlation between *Lrig2* gene dosage and the incidence and malignancy of PDGFB-induced glioma [34]. Thus, in both cervical and oligodendroglial cancer, expression of LRIG2 predicts poor survival, emphasizing that the function of LRIG2 may be different from that of LRIG1.

Expression of LRIG1 is associated with good survival in non-small cell lung cancer. LRIG1 is down-regulated in non-small cell lung cancer and lung carcinoma in situ [14,31,50] (Kvarnbrink et al., unpublished observation). Both the mRNA and protein levels of LRIG1 are associated with the survival of non-small cell lung cancer patients. In an immunohistochemical analysis of 347 non-small cell lung cancer cases, Kvarnbrink and co-workers found that high expression of LRIG1 was an independent prognostic factor that was correlated with good survival, particularly among patients with lung adenocarcinoma (Kvarnbrink et al., unpublished observation). Intriguingly, in lung squamous cell carcinoma, expression of LRIG1 was not associated with survival if only the neoplastic cells were analyzed, whereas if the stromal and immune cells were also included in the analysis, high LRIG1 expression was correlated with a better survival. In the Oncomine database, which includes composite gene expression profiles of all cell types included in the respective tumor specimens, the expression of *LRIG1* mRNA was associated with good survival in both lung adenocarcinoma and lung squamous cell carcinoma. Thus, LRIG1 expression in cancer epithelial cells and in stromal and immune cells could provide prognostic information in non-small cell lung cancer. Taken together, these findings indicate that LRIG1 could be an important prognostic factor in the two major types of non-small cell lung cancer, i.e. lung adenocarcinoma and lung squamous cell carcinoma. Furthermore, LRIG1 immunoreactivity predicted survival in a cohort that was primarily composed of early stage cases, a group of patients where new prognostic markers are especially needed.

Expression of LRIG1 shows different prognostic value depending on the clinical context in prostate cancer. Expression of LRIG1 was evaluated in a Swedish cohort of 355 men and in an American cohort of 293 men via the immunohistochemical staining of tissue microarrays [11]. The two cohorts had different clinical features and showed divergent results. In the

Swedish cohort, the patients were followed via watchful waiting, and high expression of LRIG1 was an independent prognostic factor that was associated with worse overall and disease-specific survival. The American cohort included patients who had undergone prostatectomy; in this group, the expression of LRIG1 was a positive prognostic factor for overall survival. The clinical and biological circumstances are therefore important determinants for the prognostic value of LRIG1 expression in prostate cancer.

LRIG1 expression is associated with good survival in cutaneous squamous cell carcinoma. In cutaneous squamous cell carcinoma, LRIG1 expression was investigated via immunohistochemistry in a series of 38 patients [12]. High expression of LRIG1 correlated with a higher grade of differentiation, the absence of regional or distant metastasis, and better overall survival. However, it was not investigated whether LRIG1 was an independent prognostic marker in this cohort or whether its association with survival was dependent on its correlation with histological grade or the absence of metastases.

Prognostic impact of LRIG protein and mRNA expression in other cancer types. In one study, expression of LRIG1 was evaluated in colorectal cancer via immunoblotting of the tumor and non-neoplastic tissue lysates from 30 patients [59]. LRIG1 was both up- and down-regulated; however, the available data were too limited to perform a meaningful survival analysis. As LRIG1 is a tumor suppressor in the mouse intestine, further studies to evaluate the prognostic implications of LRIG expression in human colorectal cancer may be warranted.

In a series of 31 renal cell carcinomas, *LRIG1* and *EGFR* expression was analyzed via quantitative real-time RT-PCR [60]. The *LRIG1/EGFR* ratio was reduced in renal cell carcinoma tissue compared with normal kidney cortex. In a follow-up study including 104 renal cell carcinoma cases [53], *LRIG1* expression was down-regulated in renal cell carcinoma; however, this was observed only in the clear cell subtype. There was no correlation between *LRIG1* expression and patient survival in this cohort.

In esophageal cancer, the prognostic value of the immunohistochemical expression of different LRIG proteins in tumors from 80 patients was evaluated; no significant correlations between LRIG expression and patient survival were found [61].

Ghasimi and co-workers analyzed LRIG expression in 409 meningioma cases via immunohistochemistry [62]. Expression of both LRIG1 and LRIG2 correlated with estrogen receptor status, which is consistent with the finding that LRIG1 is regulated by estrogen signaling in breast cancer [1]. Because

meningioma is usually benign, the vast majority of patients in Ghasimi's study did not succumb to their disease. Therefore, it was not surprising that no association between LRIG protein expression and meningioma patient survival was observed in this study.

A gene expression meta-analysis supports a major role for LRIG1 as a prognostic indicator in additional cancer types. In a meta-analysis of gene expression and patient outcome in nine studies of breast, lung, and bladder cancer, glioma and melanoma, *LRIG1* was identified as one of the four top genes that predicted survival across all of the data sets (the other genes were, *KIF4A*, *HJURP*, and *ESPL1*); the high expression of *LRIG1* was associated with a better prognosis for these patients [63]. This finding supports the results discussed above for breast and lung cancer, and glioma, and it also suggests that *LRIG1* expression could have prognostic value in additional cancer types including bladder cancer and melanoma. A summary of all published articles showing significant associations between LRIG gene status, mRNA expression, or protein expression and cancer patient survival is presented in Table I.

LRIG1 as a predictive marker of therapy response

LRIG1 predicts and regulates chemotherapy responses in cancer cell lines. In a series of nine esophageal cancer cell lines, expression of *LRIG1* was correlated with sensitivity to the chemotherapeutic agents cisplatin, docetaxel, and vinorelbine [61]. Consistent with this finding, ectopic expression of *LRIG1* increases the sensitivity of bladder cancer cells to cisplatin [64] and of glioblastoma cells to cisplatin and temozolomide

[29,65]. Additionally, *LRIG1* confers sensitivity of breast cancer cells to an experimental Smac mimetic inducer of apoptosis [66] and of gastric carcinoma cells to a MET-targeting antibody [32]. Taken together, these and other results indicate that *LRIG1* could have potential both as a therapeutic agent and as a predictive marker. In some of the studies referred to above, the prognostic value of *LRIG1* expression may have reflected the effects of *LRIG1* on the sensitivity of the tumors to the respective therapies used. Determination of whether the effects of *LRIG1* expression on patient survival are truly prognostic or predictive will require patient materials from controlled clinical studies including different treatment arms. The finding that *LRIG1* could serve as a predictive marker should be further investigated because there is a great need for predictive biomarkers because of the rapid increase of treatment alternatives in medical oncology.

Conclusions

The expression and gene status of *LRIG1*, *LRIG2*, and *LRIG3* have prognostic and possibly predictive value in diverse types of cancer. These markers may assist in settings of early stage cancers where current treatment decisions are often made in the absence of adequate prognostic and predictive information. It will be important to establish methods to analyze *LRIG* expression and *LRIG* gene status in the clinical setting and to investigate the clinical value of *LRIG* analyses in retrospective clinical trials with the view that *LRIG* analyses could become important when making informed and individualized clinical decisions regarding the management of cancer patients.

Table I. Correlation between *LRIG1* gene copy number status, *LRIG1* mRNA expression, or LRIG protein expression and patient survival in various cancer types.

	<i>LRIG1</i> gene copy number	<i>LRIG1</i> RNA	LRIG1 protein	LRIG2 protein	LRIG3 protein
Bladder		Good ⁶³			
Breast	Good ²	Good ^{1,2,13}			
Cervical SCC			Good ³	Poor ⁴	
Cervical adeno			Good ⁵		Good ⁵
Oligodendroglioma				Poor ¹⁰	
Glioblastoma/astrocytoma		Good ⁶³		Good ⁹	Good ⁹
HNSCC	Good ⁷		Good ⁸		
NSCLC, SCC		Good ^{63,a}	Good ^a		
NSCLC, adeno		Good ^a	Good ^a		
Prostate			Good or Poor ¹¹		
Cutaneous SCC			Good ¹²		
Malignant melanoma		Good ⁶³			

Adeno, adenocarcinoma; HNSCC, head-and-neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma.

^aKvarnbrink et al., unpublished observations.

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