

# The Role of IGF-Pathway Biomarkers in Determining Risks, Screening, and Prognosis in Lung Cancer: A Systematic Review.

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## Research

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# Abstract

**Background:** Detection rates of early-stage lung cancer are traditionally low, which contributes to inconsistent treatment responses and the highest rates of annual cancer deaths in the U.S. Currently, age and smoking history are the primary factors that qualify patients for low-dose computed tomography (LDCT) screening, which contributes heavily to a high false discovery rate. This limitation to the current screening paradigm has prompted research to identify biomarkers that will help more clearly define eligible patients for LDCT screening, differentiate indeterminate pulmonary nodules, and select individualized cancer therapy. Biomarkers within the Insulin-like Growth Factor (IGF) family have come to the forefront of this research.

**Methods:** Literature available through PubMed and Google Scholar sources was cataloged using keywords: {Lung Cancer} AND {IGF} AND {Risk OR Diagnosis OR Prognosis OR Prognostication OR Treatment}. The results were summarized and provided herein.

**Results:** Multiple biomarkers within the IGF family (or axis) have been investigated, most notably IGF-I and IGF binding protein 3 (IGFBP-3). However, newer studies seek to expand this search to other molecules within the IGF axis. Results have differed, however, due to features such as the pre-disease variable expression of IGF-I and IGFBP-3, likely promoted by factors such as obesity and smoking history. Certain studies have demonstrated these biomarkers are useful as a companion test alongside lung cancer screening, but other findings were not as conclusive, possibly owing to measurement bias from pre-analytical variables and non-standardized assay techniques. Research also has suggested IGF biomarkers may be beneficial in the prognostication and subsequent application of treatment via systemic therapy. Despite these advances, however, additional knowledge as to the intricacies of regulatory mechanisms inherent to this system are necessary to more fully harness the potential clinical utility for diagnostic tests and to identify novel targets for therapeutic intervention.

**Conclusions:** The IGF system likely plays a role in multiple phases of lung cancer; however, there is a surplus of conflicting data, especially prior to development of the disease and during early stages of detection. IGF biomarkers may be valuable in the screening, prognosis, and treatment of lung cancer, though their exact application requires further study.

## Background

Lung cancer is the leading cause of cancer deaths in the United States, with an estimated 236,000 new diagnoses and 132,000 deaths expected in 2021.<sup>1</sup> It is well established that lung cancers may present with a wide variety of phenotypic and mutational heterogeneity not only across the range of the disease, but also within specific histological subsets, such as lung adenocarcinoma. Yet, current modalities for screening and treating lung cancers employ broad guidelines that often do not account for the aforementioned molecular heterogeneity or tumor immune microenvironment, both of which may be of great importance for diagnostics and treatment plan formulation. Currently, screening for lung cancer is predicated almost exclusively on age and smoking history, while prognosis and treatment are dependent on the TNM (tumor, node, and metastasis) staging system. In more recent years, expansions to these treatment algorithms have developed as specific 'driver mutations' within cell-signaling pathways, such as EGFR, KRAS, and ALK, have been associated with

'targeted' therapeutic approaches. The pathophysiology of cancer, however, is known to be significantly more complex than even these systems acknowledge. The identification of numerous circulating biomarkers that attempt to provide further classification of these tumors promises the exploration of a new frontier in the screening and prognostication for a variety of cancers. The insulin-like growth factor (IGF) and other members of the IGF pathway, in this context, will be the point of this article.

## Methods

Literature available through PubMed and Google Scholar sources was cataloged using keywords: {Lung Cancer} AND {IGF} AND {Risk OR Diagnosis OR Prognosis OR Prognostication OR Treatment}. Manuscripts generated by these search strings were evaluated by the authors for relevance and summarized. The primary objective was to define progress in the use of members of the IGF axis of circulating factors that may aid clinical decision making.

## Results

The IGF pathway is an intricate, multi-tiered dynamic of ligands, receptor types, and cell-signaling cascades with multiple levels of regulation. Two insulin-like growth factors, IGF-I and IGF-II, play a central role in this system along with six main IGF binding proteins (IGFBPs). The IGFBPs generally regulate the actions of IGF, most commonly in an inhibitory manner upon sequestration of IGF-I from the IGF-1 receptor (IGF-1R). However, IGFBPs also modulate the activity of IGF at the receptor, thereby extending its half-life in circulation, controlling its egress from the vasculature, and influencing its clearance.<sup>2-4</sup> IGFBPs likely also independently regulate receptor activation and downstream signaling. IGFBP functions are summarized in Table 1, although it is important to note that ongoing research into their full functions is ongoing.

Table 1  
**IGFBP Functions and Major Sites of Expression**<sup>5-8</sup>

IGFBP	Function	Major Sites of Expression
1	Mostly inhibits DNA synthesis, cell growth, and differentiation. Potentiates IGF-1 action when combined with platelet-poor plasma or certain cancer cells.	Liver, placenta, and endometrium
2	Weakly potentiates and inhibits IGF activity.	Liver, pancreas, nervous system
3	Transports 90% of IGF in circulation. May sequester IGF, thus causing apoptosis. May also directly bind cell surface receptors, causing altered gene expression and altered affinity for IGF cell receptors. Functions change due to the surrounding environment (i.e., IGF levels or available cell receptors and targets)	Placenta and in large quantities in circulation.
4	Mostly inhibits IGF as well as growth of many cancers (i.e. colon cancer); donor in presence of PAPP-A	Widely expressed throughout the body, especially in ovary and liver.
5	Has inhibitory, stimulatory, and independent effects throughout the body, especially in the musculoskeletal system.	Testis, ovary, trabecular meshwork, bone, lung, uterus, placenta.
6	Mostly inhibits IGF-II and cancer growth.	Highest expression is in gonadal/reproductive tissue.

Lung cancer tissue has been well documented to differentially express multiple molecules within the IGF axis, including enhanced production of IGF-I, IGF-II, and IGF-1 receptor (IGF-1R), and lower expression of IGFBP-3.<sup>9-10</sup> Modulated expression of these molecules are highly associated with aggressive disease and poor clinical outcomes.<sup>11</sup> However, recently they have also been implicated in lung tumorigenesis.<sup>12</sup> IGF navigates its numerous effects through ligand-receptor binding and multiple downstream signaling events that increase cell proliferation, protein synthesis, and inhibition of apoptosis.<sup>13-17</sup> An overview of relevant portions of this pathway is shown in **Figure 1**. The interplay between IGF, its binding proteins, the resultant effects on IGF function, and the contributions of other members of the cellular environment constitute a complex system. It is this dynamic that lends great depth, difficulty, and promise to the study of the IGF system in cancer.

## IGF Biomarkers and Risk of Developing Lung Cancer

Delineating the risk of lung cancer development is the most important factor for the prevention and screening of the disease. Currently, the primary means of lung cancer prevention is accomplished via smoking abstinence or cessation and is further supplemented by early diagnosis via low-dose CT (LDCT) radiography to help reduce mortality.<sup>18</sup> However, LDCT scans are largely restricted to those with broad risk factors for development of disease, including age and smoking history. Due to these relatively simplified metrics, high numbers of false positive results are recorded (the false positive rate per screening round was 23.3% in the original National Lung Screening Trial (NLST)), leading to the profligate consumption of resources, expansion

of healthcare costs, and prescription of unnecessary invasive procedures (1.8% of NLST participants with a false positive result).<sup>18</sup> There is a need, therefore, for the designation of more specific risk factors that may predict the future development of lung cancer. One possibility is the use of biomarkers, such as those found within the IGF pathway. The current evidence for the selection of members of the IGF pathway as viable signposts for lung cancer diagnoses is unclear, and the lack of published reports specifically designed to measure IGF pathway family member levels prior to the diagnosis of disease presents an obstacle. In this section, only evaluations of blood samples acquired prior to diagnosis of disease, which thus assessed the actual risk of development of the cancer rather than the detection of an existing cancer, will be discussed. Establishing such experimental design parameters, unfortunately, limits the available pertinent data in the literature for a true meta-analysis, which is further complicated by conflicting results.

One prospective case-control analysis found a statistically significant, inverse association between IGF-I and the development of lung cancer in ever-smokers (HR=0.91; 95% CI, 0.86-0.96).<sup>19</sup> Multiple other presentations, however, reported no statistically significant correlation between IGF-I levels prior to diagnosis and the onset of the disease.<sup>10,20-22</sup> Two of these studies did demonstrate an elevated risk of lung cancer development with increased IGF-I levels, but the results were not statistically significant.<sup>20,23</sup> An inverse relationship between IGF-I levels and lung cancer development was described in a different paper, but this aspect ceased to be statistically significant after accounting for body mass index (BMI) and smoking history.<sup>21</sup> As such, no definitive relationship between IGF-I levels and the development of lung cancer has been proposed. Also, the non-statistically significant nature of apparent associations upon the inclusion of additional criteria, such as BMI or smoking history, signals a host of external factors likely influence IGF-I concentration prior to disease occurrence and contribute to its variable and complex expression pattern.

Five of the six previously mentioned articles also checked IGFBP-3 levels. Similar to IGF-I, no consensus was maintained among the accounts concerning how IGFBP-3 affects the development of lung cancer. An inverse relationship between IGFBP-3 and lung cancer in ever-smokers was offered in two papers, whereas another investigation revealed augmented IGFBP-3 correlated with advancement of lung cancer.<sup>10,20,23</sup> The remaining two studies demonstrated no statistically significant tendency between IGFBP-3 and initiation of lung cancer.<sup>21-22</sup> One of these trials also measured IGFBP-1 and IGFBP-2 levels, which were concluded to not be significantly related with development of lung cancer in women.<sup>22</sup> For reference, Table 2 summarizes several of these findings:

Table 2  
Results of Studies on Risk of Development of Lung Cancer.

Author	Year	Design	Cases	Controls	Time from Sample to Diagnosis	IGF-I vs. Risk of Lung Cancer	IGFBP-3 vs. Risk of Lung Cancer
Spitz, <i>et al.</i> <sup>20</sup>	2002	Nested Case-Control	159	297	3+ years	Inverse association <sup>a</sup>	Highest quartile had increased risk
London, <i>et al.</i> <sup>10</sup>	2002	Prospective Case-Control	230	659	0+ & 2+ years	NS	Inverse association <sup>b</sup>
Qian, <i>et al.</i> <sup>19</sup>	2020	Prospective Cohort	1695 ever smokers; 301 never smokers		0+ years	Inverse association <sup>b</sup>	-
Ahn, <i>et al.</i> <sup>21</sup>	2006	Nested Case-Control	200	400	5+ years	NS <sup>c</sup>	NS <sup>c</sup>
Lukanova, <i>et al.</i> <sup>22</sup>	2001	Nested Case-Control	93	186	6+ months & 3+ years	NS	NS
Ho, <i>et al.</i> <sup>23</sup>	2016	Nested Case-Control	1143 ever smokers	1143	1 year	NS	Inverse association
NS = Not significant; <sup>a</sup> Reported result of those below the age of 60 when controlling for IGFBP-3 levels; all other stratifications were not statistically significant. <sup>b</sup> Result seen only in ever smokers; <sup>c</sup> Significant difference seen until adjustment for BMI and smoking history							

Another meta-analysis examined common polymorphisms within the IGF axis, finding that certain patients had a predisposition to lung cancer due to genetic variations in IGF-I, IGF-II, IGF-1R, IGFBP-3, and IGFBP-5.<sup>24</sup> However, on subgroup analysis, the study found that this outcome was only present in the Asian population, population-based studies, hospital based studies, and PCR-RFLP (restriction fragment length polymorphism) studies, and it was not present in the Caucasian population. Therefore, this study further points towards the complexities of the IGF system prior to the development of cancer including how patient demographics and genetic make-up may influence it.

While additional research may provide greater clarity and perspective, current evidence intimates IGF markers are not beneficial in the determination of lung cancer risk, possibly due to the cross-talk of the IGF signaling pathways with other cascade highways, the impact of environmental, lifestyle, and genetic factors, or unknown stimulatory/inhibitory agents prior to the development of lung cancer.

## IGF Biomarkers and Lung Cancer Screening

The publications of the NLST results still prompted the National Comprehensive Cancer Network to recommend the administration of LDCT as the preferred screening application for the detection of lung cancer for appropriately selected high-risk patients.<sup>18,25</sup> Due to the high false positive rate, the International

Association for the Study of Lung Cancer (IASLC) and the Strategic CT Screening Advisory Committee (SSAC) advised the utilization of blood-based biomarkers to assist current LDCT screening.<sup>26</sup> Multiple efforts to establish a “liquid biopsy” capable of reducing false-positives screens, prognosticating risk of developing cancer, and navigating patient care have been initiated. Of the potential biomarkers identified, candidates within the IGF pathway have emerged as contenders. However, the literature is replete with non-standardized techniques and conflicting results, causing difficulty in formulating definitive conclusions at this time.

Despite, IGF’s apparent lack of utility in determining risk of lung cancer, multiple reports have discovered elevated serum or plasma IGF-I concentrations in patients with existing primary lung cancers.<sup>27–32</sup> Four investigations were cross-sectional, and two prospective cohort studies totaled approximately 500 case subjects. Participant serum or plasma was analyzed via enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or immunoradiometric assay (IRMA), with the majority of the trials analyzing serum samples via ELISA. Most inquiries encompassed non-small cell lung cancer (NSCLC), while one investigation also included small cell lung cancer (SCLC).<sup>28</sup> The key message from these interrogations was the apparent elevations in IGF-I levels in relation to tumor size, advanced tumor stage, and metastatic propensity. A statistically significant difference between histological subtypes of lung cancer was not revealed.

Trials that concerned IGFBP-3 typically described lower levels of the binding protein in all lung cancers. Also, heightened differences were observed between IGF-I and IGFBP-3 levels in control participants compared to enrollees who had a higher T stage; revealed cancer of the lymph nodes; and demonstrated evidence of metastases.<sup>33,30–32</sup> A synopsis of the results stipulates IGF-I generally increases with lung cancer, especially individuals diagnosed with advanced disease, while IGFBP-3 decreases. This phenomenon may be a consequence of the ability of IGFBP-3 to bind IGF-I, thereby suppressing its proliferative and anti-apoptotic functions. Therefore, a coinciding reduction of IGFBP-3 and elevation of IGF-I may permit increased tumor growth to occur. Although the cause-effect dynamic of these two potential biomarkers and the instigation of cancer is still not well-established, the cited studies seemingly suggest the future employment of these biomarkers for screening in lung cancer.

This relationship is not as obvious, however, as the above citations may surmise. Other publications contradict the previously mentioned generalization with reports of lower concentrations of IGF-I in the serum of lung cancer patients.<sup>33–34</sup> Notably, one of these counterposing papers included a much larger patient sample size than the encounters listed above (224 case subjects and 123 controls), indicating a greater statistical power.<sup>33</sup> This manuscript, similarly, demonstrated highly significant ( $p < 0.001$ ) lower circulating levels of IGF-II, IGFBP-3 and IGFBP-5 in the plasma for screening cases with malignancies versus those with benign pulmonary nodules. Further and more intensive analyses, therefore, are necessary to dissect any relationship or concentration-dependent conjunction of these putative members of the IGF family. A 2012 meta-analysis examined the data from six nested case-control groups and eight case-control studies to discern the association between IGF-I and IGFBP-3 levels and the presence of lung cancer. No statistically significant correlation between IGF-I levels and the presence of lung cancer was detected. The analysis did, however, indicate a statistically significant, inverse relationship between IGFBP-3 levels and the existence of lung cancer.<sup>35</sup> Although a reconciliation of the discrepancy presented in prior publications for IGF-I levels was not

achieved, the consideration of IGFBP-3 as a potential biomarker for lung cancer was further supported. Table 3 lists a brief summary of major papers on this topic.

Table 3  
Results of Papers Studying Detection of Lung Cancer

Author	Year	Design	Cases	Controls	Sample	Method	IGF-I Status	IGFBP-3 Status
Tisi, <i>et al.</i> <sup>29</sup>	1991	Cross-Sectional/ Cohort	46	38	Serum	RIA	↑	-
Wang, <i>et al.</i> <sup>31</sup>	2013	Cross-sectional	57	17	Serum	ELISA	↑	↓
Fu, <i>et al.</i> <sup>27</sup>	2013	Prospective Cohort	80	45	Serum	ELISA	↑	-
Izycki, <i>et al.</i> <sup>28</sup>	2004	Prospective Cohort	38	10	Serum	ELISA	↑	-
Reeve, <i>et al.</i> <sup>34</sup>	1990	Cross-Sectional	52	63	Serum	RIA, IRMA	↓	-
Yu, <i>et al.</i> <sup>32</sup>	1999	Cross-Sectional	204	218	Plasma	ELISA	↑	↓ <sup>d</sup>
Cao, <i>et al.</i> <sup>35</sup>	2012	Meta-Analysis	401	343	Mixed (mostly Serum)	RIA, ELISA, IRMA	NS	↓
Kubasiak, <i>et al.</i> <sup>33</sup>	2014	Cross-Sectional	224	123	Mixed (serum/plasma)	Luminex	↓	↓
NS= Not significant; RIA= Radioimmunoassay; ELISA= Enzyme-linked immunosorbent assay; IRMA= Immunoradiometric assay ↑ = Higher levels seen in lung cancer ↓ = Lower levels seen in lung cancer <sup>d</sup> Result after adjustment for IGF-I level								

Considerable concerns underlying the aforementioned results must be noted. These disclaimers include the combination of data from a number of trials that isolated serum and plasma with different protocols and the incomplete description of the methodology (duration of sample storage prior to centrifugation; types of reagents that dissociated the IGF from its binding partner; the possible application of IGF-II to prevent re-association; etc.) had a significant impact on analytical results. That is, pre-analytical variables in the matrix of choice have been shown to alter IGF-I level measurement.<sup>36</sup> Although serum and plasma are similar in composition, plasma includes the soluble proteins responsible for blood clotting, whereas blood that has undergone the myriad of proteolytic steps that constitute the clotting cascade forms serum. Additionally, specific details of procedures and types of anti-coagulants may vary, possibly influencing which metabolites

may remain in the processed sample. One study indicated data point reproducibility is high within the same procedure, but serum tends to contain higher metabolic concentrations than plasma and is thus more sensitive for biomarker analysis.<sup>37</sup> A separate paper specifically showed the effect elicited by different isolation procedures: Samples were either treated with an acid extraction solution that induced IGF-IGFBP complex dissociation as a method to detect total IGF-I in the blood, serum, or plasma or remained untreated. The unextracted (non-dissociated) serum contained markedly elevated IGF-I when compared to controls, while the extracted (dissociated) serum did not, suggesting a significant source of potential measurement bias.<sup>34</sup> Such a fundamental difference either between serum and plasma or the protocols applied to them may account for some of the variance between studies and create complications in the comparison or combination of current data sets. Current practice makes unextracted serum inappropriate for IGF measurement, but much of the current data was gathered prior to this normalization.

In 2011, the first international consensus statement on the measurement of IGF was released.<sup>38-39</sup> The consortium encouraged the uniform use of the IS 02/254 WHO reference standard for IGF assays, the choice of serum for test samples, a delay of no more than two hours from blood acquisition to centrifugation, the commitment to a validated method for preventing IGFBP interference, and the consideration of multiple IGF measurements due to intra-individual imprecision. Therefore, as more studies are performed with consistent adherence to these guidelines, it is possible less discordance will exist among the data, and a more clearly defined role for IGF biomarkers in lung cancer screening will develop.

Biomarker research in recent years has shifted towards the use of IGFBPs outside of IGFBP-3, which may potentially widen the array of biomarkers within the IGF system for lung cancer detection. A 2021 study found higher levels of IGFBP-4 in all stages of disease and histologic subgroups of lung cancer when compared to healthy individuals. It is also important to note that pregnancy-associated plasma protein A (PAPP-A) has proteolytic activity on IGFBP-4, so the study also measured these levels. Although PAPP-A levels did appear to be higher in untreated lung cancer patients when compared to healthy controls, these results were not statistically significant.<sup>40</sup> Additionally, IGFBP-2 has been studied in association with anti-IGFBP-2 autoantibodies in lung cancer. Notably, the highest sensitivity (85.7%) of these biomarkers for the diagnosis of lung cancer was seen when the autoantibodies and IGFBP-2 were used in combination.<sup>41</sup> A 2014 study that measured levels of IGF-I, IGF-II, and IGFBPs 1-7 found that IGFBP-5 and IGF-II levels were higher in benign tumors than in NSCLC.<sup>33</sup> Based on these recent studies, it is clear that the IGF system is full of potential biomarkers that warrant further study outside of the previously mentioned IGF-I and IGFBP-3.

Due to the complexity of the IGF system, the complexities and indeterminate nature of the tumor immune microenvironment, and the intricate interplay between the two, a few laboratories have attempted to manufacture panels of biomarkers that can better detect lung cancer. One group obtained 122 samples from patients with NSCLC and compared them to 225 healthy control samples.<sup>42</sup> Thirty previously tested analytes that demonstrated promise as biomarkers were determined via the random forest method. The top five ranked biomarkers, IGF-I, A1AT, CYFRA 21-1, RANTES, and AFP, were incorporated into a multi-analyte panel. This collection was then applied to a validation cohort of 21 NSCLC patients and 28 healthy control patients, in which it distinguished NSCLC patients from control patients at approximately 90% accuracy.<sup>42</sup> Another team specifically investigated the difference in levels of IGF-I, IGF-II, and IGFBP 1-7 between patients diagnosed with

NSCLC (n=224) and participants with benign pulmonary nodules (n=123), as discovered on low-dose CT scans.<sup>33</sup> Analysis of differences in the IGF pathway biomarkers of the two cohorts spurred the application of samples into a multi-analyte kit constituting IGFBP-4, IGFBP-5, IGF-II, interleukin-6, interleukin-10, interleukin-1 receptor antagonist, and the stromal cell-derived factor-1 (SDF-1a+b). This test produced a negative predictive value of 100% on validation.<sup>33</sup> These studies add credence to the idea that increased usage of IGF pathway biomarkers may increase the utility of biomarker panels in lung cancer screening. However, additional and larger studies will be needed to corroborate these findings and to solidify the predictive capabilities of their levels.

## IGF Biomarkers and Prognosis in Lung Cancer

In addition to screening, a number of possible members of the IGF pathway have been postulated as having potential prognostic or predictive value pertaining to disease progression or treatment efficacy. Although IGF-I and IGFBP-3 have been emphasized regarding the categories of lung cancer risk and associated screening, additional biomarkers emerge during the course of the disease that may also accurately convey such an appraisal, including other IGFBPs, insulin receptor substrate (IRS)-1, IRS-2, and IGF-1R.

The reduction of the IGF-I/IGFBP-3 ratio in NSCLC patients who responded to first-line treatment suggested such a metric could be a valuable predictor of response to chemotherapy in these patients.<sup>43</sup> The association of high IGF-I levels with advanced stage disease, larger tumor diameter, and shorter survival was also indicative of these characteristics. Additionally, patient IGF-I levels were depressed following resection of NSCLC tumors, further demonstrating IGF-I as a prognostic biomarker that could be measured throughout the course of disease.<sup>9</sup> Increased IGFBP-3 levels prior to treatment with irinotecan and cisplatin chemotherapy were affiliated with improved prognoses in NSCLC patients with advanced disease, implicating a potential role of IGFBP-3 as a predictive biomarker.<sup>44</sup>

The mediation of the expression of signaling components by IGF-I may be related to phenotypic transdifferentiation of the cancer cells via the epithelial-to-mesenchymal transition (EMT) spectrum, whereby tumor cells tend to lose adhesion to surrounding cells, thus increasing motility, invasion and metastasis of epithelial tumors.<sup>45-46</sup> The elevation of IGF-I and IGF-1R and their resultant interaction appears to up-regulate the PI3K/AKT/NF- $\kappa$ B pathway with the concomitant activation of ZEB2 and SNAIL1, altering protein expression and the EMT phenotype in certain lung cancers.<sup>45</sup> The extended interplay of stimulatory and inhibitory checkpoints of the intracellular avenues of the IGF pathway is certainly more heavily regulated and interspersed with cross-pathway entrance ramps than such simplified explanations imply, but a full discussion of this pathway and the differences between cancer types is beyond the scope of this review. The general concept persists, however, of a paradigm in which IGF-I may directly effect the expression of other members of the IGF system, which may subsequently be used to determine overall prognosis and response to future treatments.

Additional potential candidates that may develop during the course of disease include IGF-1R, IRS-1, and IRS-2. Multiple meta-analyses of NSCLC patients correlated augmented expression of IGF-1R with worse disease-free survival (DFS).<sup>47-48</sup> No description, however, was delineated between overall survival (OS) and IGF-1R levels in NSCLC and SCLC. It is speculated inconsistencies in IGF-1R measurement techniques and variance of

treatment between patients may have impacted the lack of findings in relation to OS.<sup>47</sup> Another study highlighted the coincidence of IRS-1 suppression and IRS-2 elevation, both significant substrates of IGF-1R, which was associated with worse outcomes in NSCLC.<sup>49</sup>

As previously mentioned, most IGFbps exhibit some utility in prognostication as well. One study linked IGFBP-1 to poor OS in lung adenocarcinoma.<sup>50</sup> IGFBP-1 was evaluated in a seven-analyte panel to identify patients with disease recurrence following resection of node-negative NSCLC tumors that were less than 4 cm in size. The panel proved to be 91% sensitive and had a negative predictive value of 83%.<sup>51</sup> Multiple papers have demonstrated that higher levels of IGFBP-2 are associated with worse OS in lung adenocarcinoma, squamous cell carcinoma, and small cell carcinoma, and these higher levels are associated with increased rates of metastasis and higher staging.<sup>50,52-53</sup> However, one of these studies did associate high IGFBP-2 levels with favorable OS in patients with squamous cell carcinoma.<sup>50</sup> Results for IGFBP-4 have shown some discrepancy between in vivo and in vitro studies. Two in vivo studies indicated poor prognostic associations with IGFBP-4, including worse OS and shorter median survival.<sup>50,54</sup> In vitro studies have shown anti-tumor effects of IGFBP-4 in NSCLC.<sup>55</sup> Multiple studies showed an inverse association between IGFBP-5 and prognostic indicators, including OS in patients with lung squamous cell carcinoma, nodal status, and disease recurrence, and recurrence-free survival.<sup>50,56</sup> High IGFBP-7 was also associated with spread to regional lymph nodes, but was dissociative with respect to recurrence-free survival.<sup>56-57</sup> Finally, IGF2BP3 has shown an association with poor OS in lung adenocarcinoma.<sup>58-59</sup> Though previous investigations insinuated some viability of IGFbps in the prognostication of lung cancer, expanded clarity and a more extensive mapping of which IGFbps are the most effective and potent markers for the prognostication of different types of lung cancer still remains to be ascertained. Future cases must concentrate on the concatenation of prognoses with regard to treatment strategies.

The ability of IGF biomarkers to serve as chaperones to the response to specific therapies has been proposed. For example, IGF-independent effects have also been observed in lung cancer resistance. IGFBP-2 appears to stimulate growth and is aligned with NSCLC resistance to dasatinib, a tyrosine kinase inhibitor (TKI), a group of drugs that interfere with tyrosine kinases, enzymes responsible for the propagation of cell signaling pathway activation.<sup>60</sup> Decreased IGFBP-3 in the peritumoral environment in NSCLC establishes a resistance to EGFR-TKIs, such as gefitinib and erlotinib, as well as cisplatin-resistant tumors. Also, diminished IGFBP-7 imbues NSCLC tumors with apparent cisplatin-resistant attributes.<sup>61-63</sup> Such evidence supports the notion that the presence or absence of IGFbps may predict tumor response to selected therapies.

IGF-1R is also predictive of response to treatment, as demonstrated by the apparent up-regulation in IGF-1R in patients with NSCLC who have developed a resistance to gefitinib, an epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI).<sup>64</sup> It has been postulated this activation of the IGF system is a reactive compensatory mechanism due to the inhibition of EGFR by gefitinib. The exact nature of the cross-talk between these classic signaling cascades is likely a more complex interplay that is further confounded by the participation of the underlying tumor immune microenvironment. Also, the aforementioned IGF-1R-induced EMT may instigate resistance to erlotinib, another EGFR-TKI.<sup>65</sup> The accumulation of the data thus posits IGF-1R levels may help predict treatment response to a number of EGFR-TKIs.

The action of the putative inhibitor of IGF-1R as it relates to chemotherapeutic responsiveness has also been elaborated. The inhibitory hindrance of IGF-1R allowed gefitinib to reclaim some of its apoptotic and anti-proliferative properties in gefitinib-resistant NSCLC cell lines.<sup>66</sup> Similar findings relevant to circulating members of the IGF axis were also noted in the literature.<sup>67</sup> More recent human trials of a number of different IGF-1R inhibitors, however, display conflicting results. It is important to note that more than ten IGF-1R inhibitors, with varying structures/mechanisms, including TKIs and monoclonal antibodies, have been applied in clinical trials. The combination of these inhibitory factors with different chemotherapy agents has sparked varying degrees of success. Most of these trials did not reveal great efficacy in the treatment of lung cancers; however, patients typically were not selected based on specific biomarker levels.<sup>68</sup> For example, a cohort that combined Figitumumab, a monoclonal antibody targeting IGF-1R, with paclitaxel and carboplatin to combat advanced NSCLC generated greater progression-free survival in patients with squamous cell carcinoma during phase 2 trials, but increased deaths of subjects in phase 3 trials. The division of patient groups by the level of expressed IGF-I yielded two distinct groups: Patients with higher IGF-I levels had better outcomes and OS relative to the control group, while participants with low IGF-I levels showed worse OS compared to the control group.<sup>69</sup> A predictive pattern regarding IGF-I-associated response to treatment was therefore pronounced, and the corresponding selection of the proper patient populations for use, as well as an identification of a contraindication may be applicable in certain patients.

Although the fluid cause-effect ecosystem between IGF signaling cascades and chemotherapy resistance glides between cresting and crashing waves of stimulation and inhibition that seem to simultaneously augment and cancel each other, many of these biomarkers may be clinically practical for the prediction of the response in targeted or individualized therapies.

## Discussion

The role of the IGF pathway in the development, recurrence, or defeat of lung cancer, and its corresponding use in prediction, detection, and prognostication of disease is at the nexus of complex signaling cascades, numerous external factors, and a host of genomic, proteomic, and metabolomic parameters. This review examined a collection of previous studies that analyzed IGF pathway molecules as potential biomarkers for risk of development of disease; unfortunately, has neither been able to conclusively describe the definitive actions of such molecules, nor resolve the significance of the pathway with respect to the disease onset or progression. Despite the acknowledged limitations, the inclusion and combination of members from the IGF axis in panels of biomarkers and with LDCT scans have strengthened the efficacy of lung cancer detection methodologies and show great promise for inclusion in biomarker panels aimed at improved clinical decision making. Nevertheless, further research with a focus on a wider range of molecules within the IGF system and larger sample sizes are required to confirm these results. Until the coordinated integral standardization of assay protocols has been implemented, refined, and incorporated into large-scale and generalizable studies, the current data is merely a source of speculative guidance regarding real-world treatment tactics and strategies. If such procedural advancements do occur, the realization of IGF biomarkers as potential ambassadors of therapy or agents of surveillance against and of the disease could radically alter the landscape of lung cancer diagnostics, prognostics, and treatment. Such aspirations can only be achieved with

continued federal funding to support further research, development, and implementation of these systems into lung cancer detection and treatment modalities.

## Conclusions

The IGF axis encompasses a range of circulating and cell-surface molecules that represents one of the central pathways in metabolic regulation with demonstrated significance to tumor biology. Biomarkers from this pathway, likely as a member of a complex panel of biomarkers aimed at evaluating multiple facets of tumor behavior, have great promise to contribute to our ability to guide clinical decision making in lung cancer detection and prognostication. Delineating the nuances of this system in a disease-specific manner with greater insights into biological functions of these components, will promote the development of these novel diagnostics and provide a foundation for new lead agents for therapeutic interventions.

## Abbreviations

- Low-dose Computed Tomography (LDCT)
- Insulin-like Growth Factor (IGF)
- Insulin-like Growth Factor binding protein (IGFBP)
- Tumor, node metastasis (TNM)
- Insulin-like Growth Factor 1 receptor (IGF-1R)
- Insulin Receptor Substrate (IRS)
- B Cell Lymphoma-2 (Bcl2)
- Tumor immune microenvironment (TME)
- National Lung Screening Trial (NLST)
- International Association for the Study of Lung Cancer (IASLC)
- Strategic CT Screening Advisory Committee (SSAC)
- Enzyme-linked immunosorbent assay (ELISA)
- Radioimmunoassay (RIA)
- Immunoradiometric assay (IRMA)
- Non-small cell lung cancer (NSCLC)
- Small cell lung cancer (SCLC)
- Epithelial-to-mesenchymal transition (EMT)
- Disease free survival (DFS)
- Overall survival (OS)
- Tyrosine kinase inhibitor (TKI)
- Epidermal growth factor receptor (EGFR)

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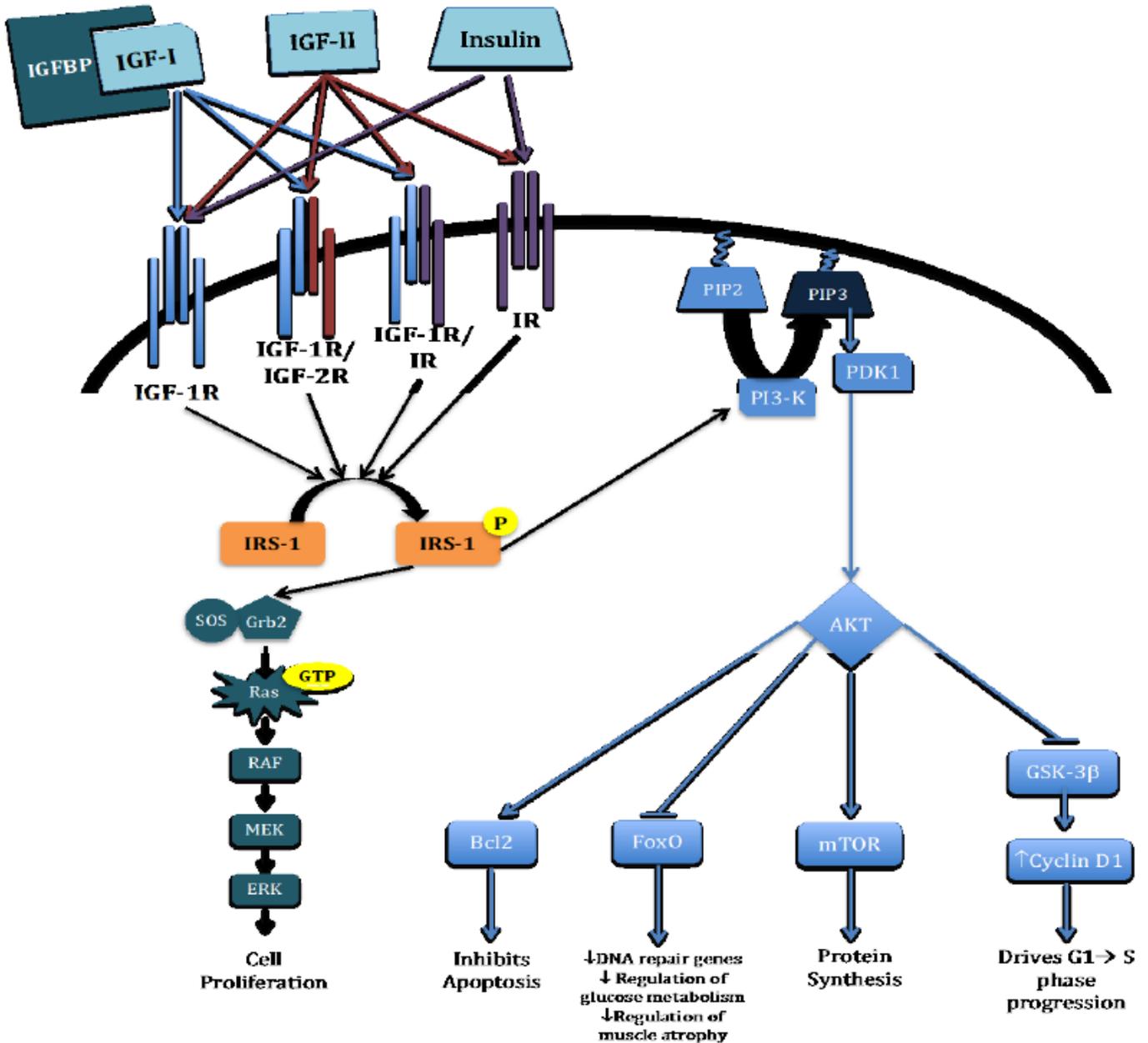
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## Figures



**Figure 1**

IGF cascade. Broad overview of the IGF pathway and its downstream effects on cell survival and proliferation. Briefly, binding of IGF-I to IGF-1R begins the cascade via two separate pathways via phosphorylation of IRS-1. The K-Ras/BRAF/MEK/MAPK pathway increases cell proliferation. The PI3-K/AKT pathway affects several downstream regulators that have varying effects within the cell. Stimulation of Bcl2 inhibits apoptosis; inhibition of FoxO diminishes DNA repair, regulation of muscle atrophy, and alters glucose metabolism; activation of mTOR promotes protein synthesis; and abrogation of GSK-3 $\beta$  increases Cyclin D1 levels, resulting in phase progression in the cell cycle.<sup>13-16</sup>