FGFR2b: An Emerging Target in Gastric Cancer

Objectives

1. Highlight the unmet needs and complex heterogeneity in gastric cancer
2. Review the role of the FGFR2b protein as an emerging biomarker in gastric cancer and its role in precision medicine
3. Describe the role of the FGFR2b protein overexpression in tumorigenesis and its potential as a therapeutic target
4. Demonstrate how testing for FGFR2b using IHC can be integrated into future pathological testing workflows

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; IHC, immunohistochemistry.

Gastric Cancer:
Unmet Need and Complex Heterogeneity

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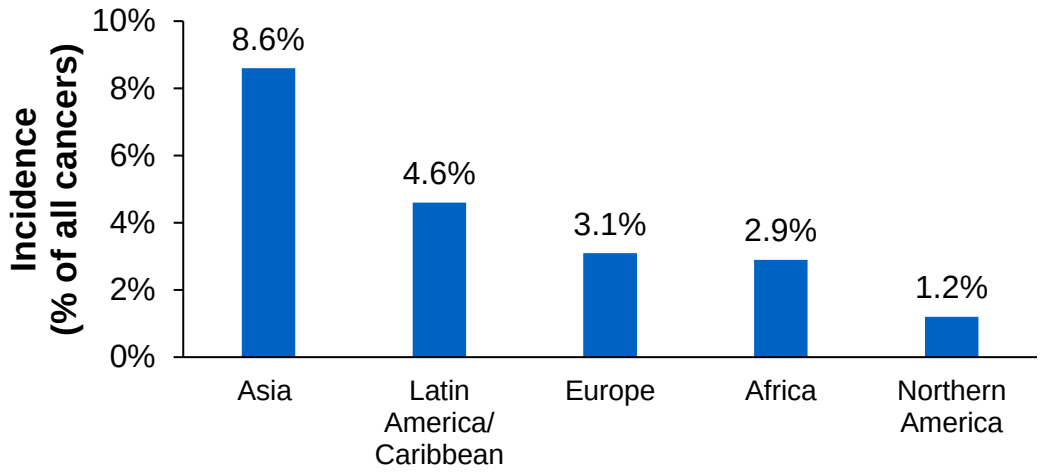
Gastric Cancer Is the Fourth Leading Cause of Cancer-Related Death Worldwide [1]

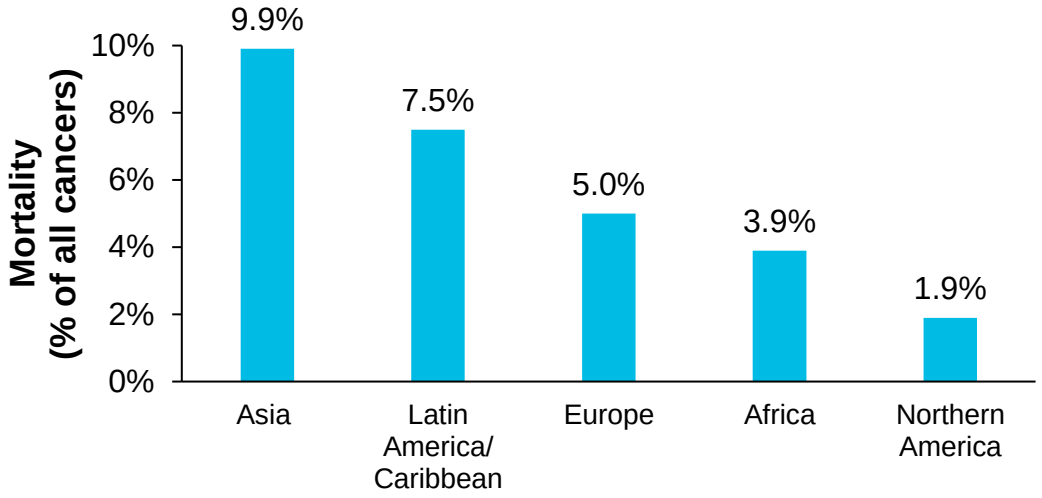
1 million **new cases** of gastric cancer are diagnosed globally each year [1,*]

769,000 **deaths** are caused by gastric cancer globally each year [1,*]

Gastric Cancer Incidence (2020) [2,*]



Gastric Cancer Mortality (2020) [2,*]



The global incidence of and mortality due to gastric cancer remains a significant unmet need

*Based on GLOBOCAN 2020 data. [1]

1. Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249. **2.** World Health Organization. www.gco.iarc.com. Accessed February 11, 2022.

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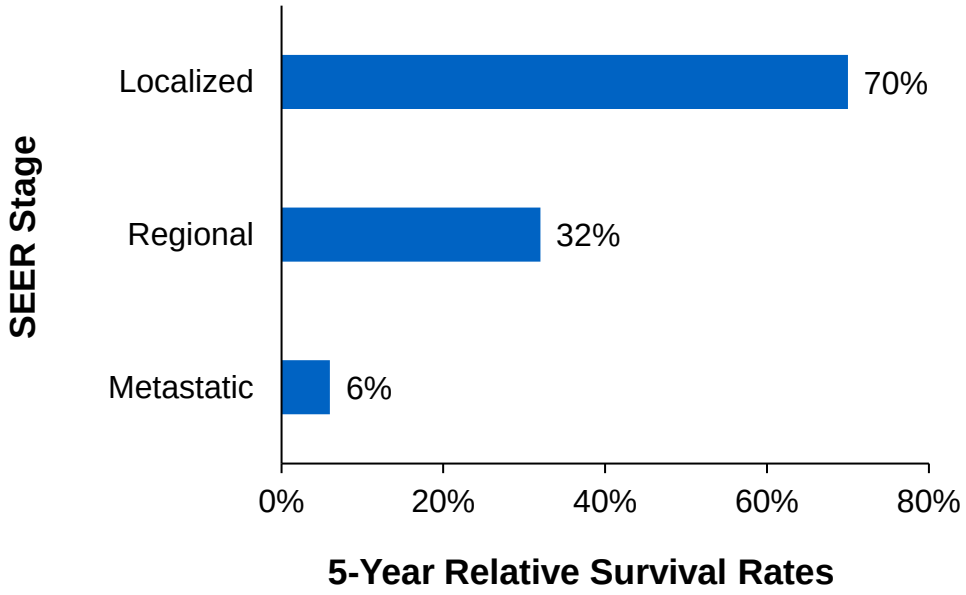
Most Patients With Gastric Cancer Are Diagnosed at an Advanced Stage With Low Rates of Survival

5-Year Relative Survival Rates by Stage at Diagnosis From 2010-2016 (US) [1]



> 50% of patients with gastric cancer in the United States present with **advanced-stage disease** at the time of diagnosis [2,*]

While signs and symptoms of early disease may be difficult to spot, leading to delays in diagnosis and poor survival, earlier detection of cancer may improve outcomes due to the ability to intervene earlier [1,3]

*Advanced stage defined as regionally advanced (stage 3) and metastatic (stage 4). Data from a retrospective study involving > 50,000 patients with gastric cancer. [2]

US, United States; SEER, Surveillance, Epidemiology, and End Results program.

1. American Cancer Society. www.cancer.org. Accessed February 11, 2022. **2.** Hundahl SA, et al. *Cancer*. 2000;88:921-932. **3.** GBD 2017 Stomach Cancer Collaborators. *Lancet Gastroenterol Hepatol.* 2020;5:42-54.

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Gastric Cancer Can Be Attributed to Multiple Environmental and Genetic Risk Factors

H. pylori	*H. pylori* infections are the main cause of gastric cancer, accounting for ~ 89% of cases [1]
Age	In addition to the rising incidence and risk of age-related disease due to the increase in global life expectancy,[2] incidence rates are also increasing among younger populations in countries with historically low-incidence [3]
Sex	Gastric cancer is 2 times more likely to develop in males than females [4]
Obesity	The rapid increase in the global prevalence of obesity, which may induce stomach lining inflammation, is linked to an increase in gastric cancer burden [5,6]
Diet and Alcohol	High salt content, preserved foods, and > 3 alcoholic drinks per day can increase the risk of gastric cancer [7]
Genetics	Inherited genetic mutations,* family history of gastric cancer, and type A blood are associated with a higher risk of gastric cancer [5,7]

While aging and other risk factors (eg, obesity, diet, sex, genetics) contribute to gastric cancer, incidence is also increasing among younger populations [8]

*Including mutations in *CDH1, MLH1, MSH2, APC, TP53, STK11,* and *EPCAM*. [9]

APC, adenomatous polyposis coli; CDH1, cadherin-1; EPCAM, epithelial cellular adhesion molecule; MLH1, mutL homolog 1; MSH2, mutS homolog 2; STK11, serine/threonine kinase 11; TP53, tumor protein 53.

1. Balakrishnan M, et al. *Curr Gastroenterol Rep*. 2017;19:36. **2.** Lee SR, et al. *J Korean Surg Soc*. 2012;82:211-218. **3.** Arnold M, et al. *Gut.* 2020;69:823-829. **4.** Sung H, et al. *CA Cancer J Clin.* 2021;71:209-249. **5.** Rawla P, et al. *Prz Gastroenterol*. 2019;14:26-38. **6.** Karczewski J, et al. *Dig Dis Sci.* 2019;64:2740-2749. **7.** American Cancer Society. www.cancer.org. Accessed November 22, 2021. **8.** Schell D, et al. *Cancers.* 2022;14:275.

Gastric Cancer Is a Complex and Heterogenous Disease

Classification Parameters: [1,2]

Anatomical location

- Noncardia
- Cardia

Histology

- Intestinal/well-differentiated
- Diffuse/undifferentiated

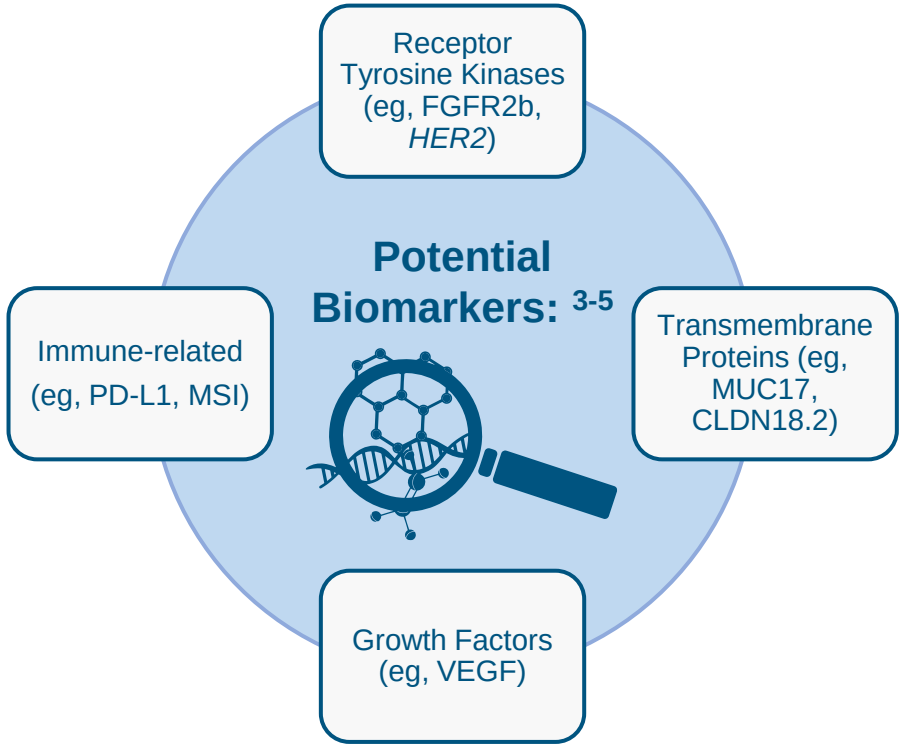
Etiology

- Sporadic
- Familial predisposition

Molecular Characteristics: [3]

- **EBV-positive**
- **Microsatellite Instability**
- **Genomically Stable Tumors**
- **Chromosomal Instability**

Potential Biomarkers: [3-5]



Research into the understanding of the heterogeneity of gastric cancer has the potential to identify clinical and therapeutic biomarkers [3]

CLDN18.2, claudin-18 isoform 2; EBV, Epstein-Barr virus; FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; MUC17, mucin 17; PD-L1, programmed cell death ligand 1; VEGF, vascular endothelial growth factor.

1. Rawla P, et al. *Prz Gastroenterol.* 2019;14:26-38. **2.** De Mello RA, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:249-261. **3.** The Cancer Genome Atlas Network. *Nature.* 2014;513:202-209. **4.** Fontana E, et al. *Ther Adv Med Oncol.* 2016;8:113-125. **5.** Yang B, et al. *J Exp Clin Cancer Res.* 2019;38:283.

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Biomarkers in Gastric Cancer and a Path for Precision Medicine

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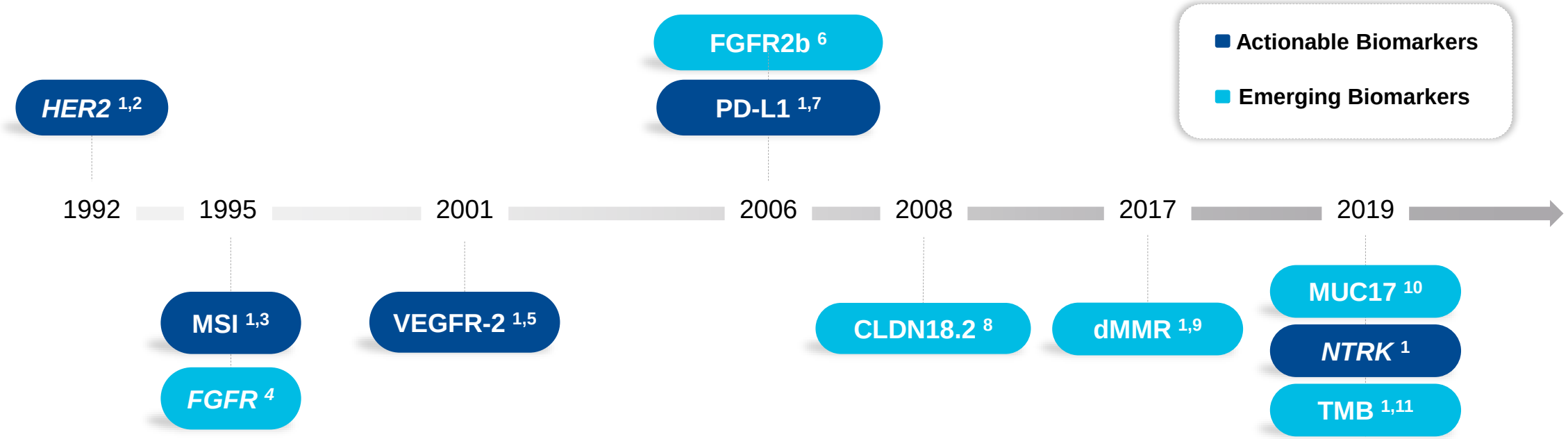
Identification of Potential Gastric Cancer Biomarkers Has Prompted the Investigation of Targeted Therapies

Appearance of Gastric Cancer Biomarkers in Peer-Reviewed Literature



FGFR2b is among several emerging biomarkers in the gastric cancer landscape that are under clinical investigation [12]

CLDN18.2, claudin-18 isoform 2; dMMR, mismatch repair deficient; FGFR, fibroblast growth factor receptor; FGFR2b, FGFR 2, isoform IIIb; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; MUC17, mucin 17; NTRK, neurotrophic tyrosine receptor kinase; PD-L1, programmed cell death ligand 1; TMB, tumor mutational burden; VEGF, vascular endothelial growth factor receptor 2.

1. ACS. www.cancer.org, Accessed February 15, 2022. **2.** Jaehne J, et al. *J Cancer Res Clin Oncol.* 1992;118:474-479. **3.** Nakashima H, et al. *Int J Cancer.* 1995;64:239-242. **4.** Ueki T, et al. *J Pathol.* 1995;177:353-361. **5.** Tian X, et al. *Biochem Biophys Res Commun.* 2001;286:505-512. **6.** Matsunobu T, et al. *Int J Oncol.* 2006;28:307-314. **7.** Wu C, et al. *Acta Histochem.* 2006;108:19-24. **8.** Sahin U, et al. *Clin Cancer Res.* 2008;14:7624-7634. **9.** Le D, et al. *Science*. 2017;357:409-413. **10.** Yang B, et al. *J Exp Clin Cancer Res.* 2019;38:283. **11.** Samstein RM, et al. *Nat Genet*. 2019;51:202-206. **12.** Ahn S, et al. *Mod Pathol.* 2016;29:1095-1103.

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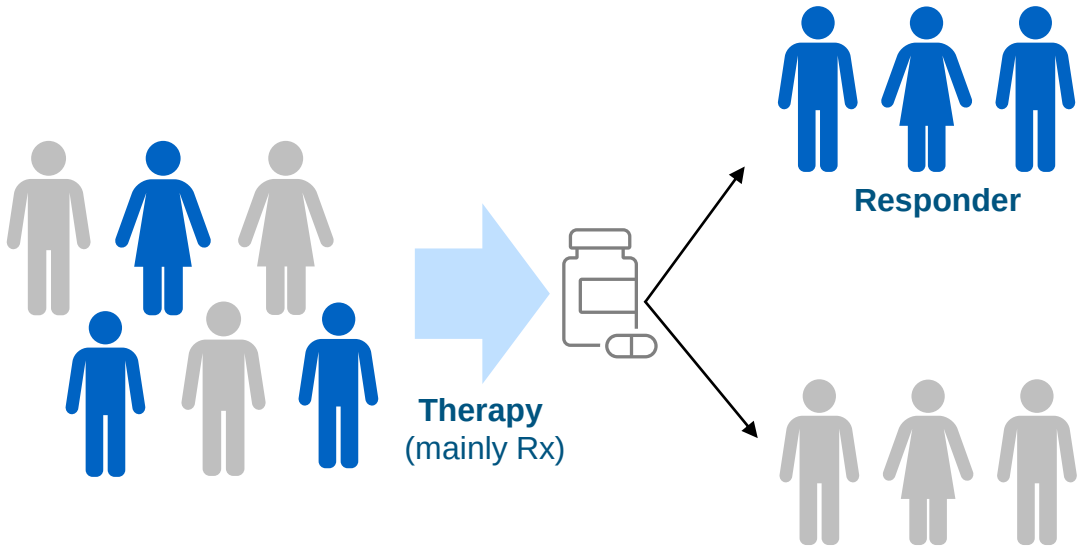
Targeted Therapies May Improve Outcomes for Patients With Metastatic Gastric Cancer [1]

Traditional Medicine [2,3]

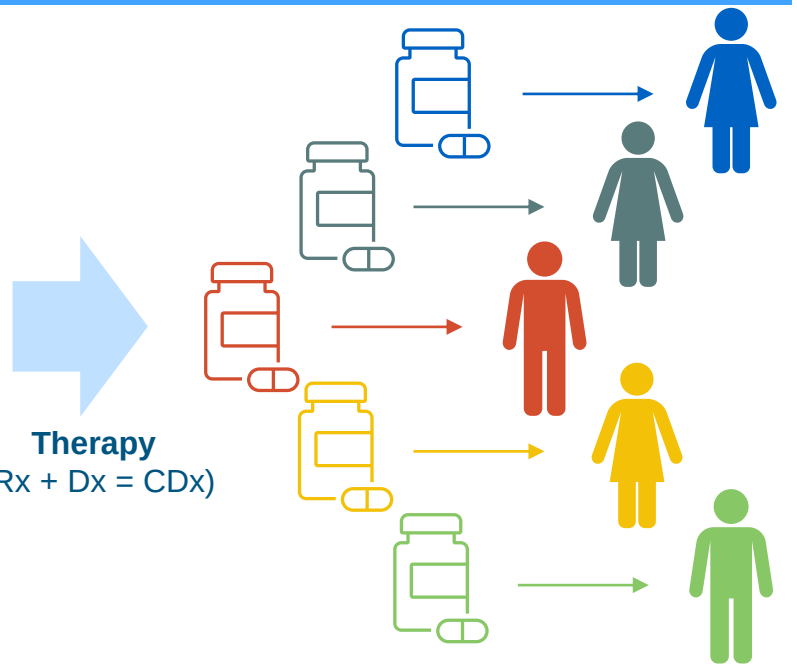


A "one-size-fits-all" approach that overlooked molecular profiling

Precision Medicine [2,3]

Individual patient level:
- Genomics and Omics
- Lifestyle
- Preferences
- Health History
- Medical Records
- Compliance
- Exogenous Factors

Companion Diagnostic (CDx):
- IHC
- FISH
- NGS



Each patient benefits from individualized treatment

Testing patients with metastatic G/GEJ cancer for actionable and emerging biomarkers can provide insight into a patient's likelihood of responding to targeted therapies [4,5]

Dx, diagnosis; FISH, fluorescence in situ hybridization; G/GEJ, gastric/gastroesophageal junction; IHC, immunohistochemistry; NGS, next-generation sequencing; Rx, medical prescription.

1. Salati M, et al. *ESMO Open.* 2017;2:e000206. **2.** Malone E, et al. *Genome Med.* 2020;12:8. **3.** Forbes. www.forbes.com. Accessed January 21, 2022. **4.** American Cancer Society. www.acs.org. Accessed February 8, 2022. **5.** Catenacci DVT, et al. *Future Oncol.* 2019;15:2073-2082.

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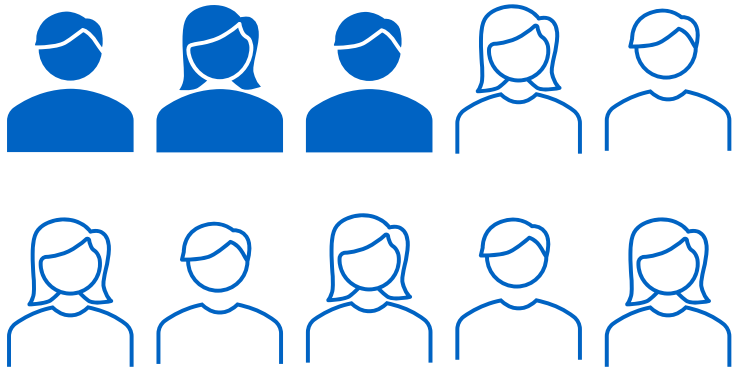
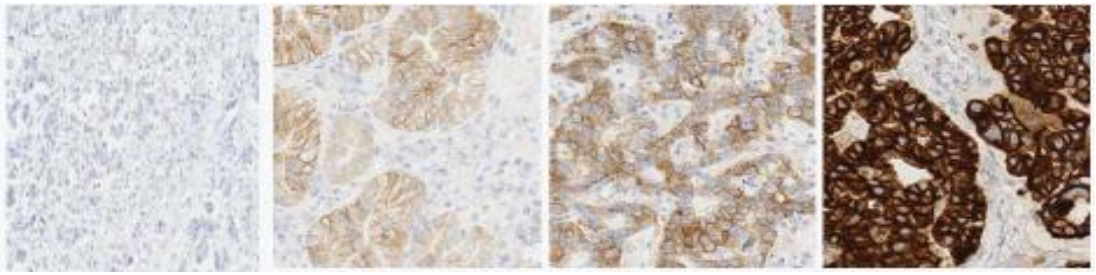
FGFR2b Expression in Tumorigenesis

FGFR2b Protein Is Overexpressed in Some Patients With Gastric Cancer and May Be Associated With Poor Prognosis



~ 3 in 10 patients with metastatic G/GEJ cancer overexpress the FGFR2b protein [1,*]

FGFR2b Protein Overexpression by IHC Is Defined as 2+/3+ Staining [1]



No staining (0) | Low–Moderate (1+) | Moderate–Strong (2+) | Strong (3+)

- FGFR2b overexpression was more frequent in tumors with poorly differentiated ($P < 0.001$) and diffuse type histology ($P = 0.10$) [2,†]
- Patients with FGFR2b-overexpressed gastric cancer and an H-score‡ ≥ 150 showed significantly shorter overall survival ($P = 0.001$) [2]

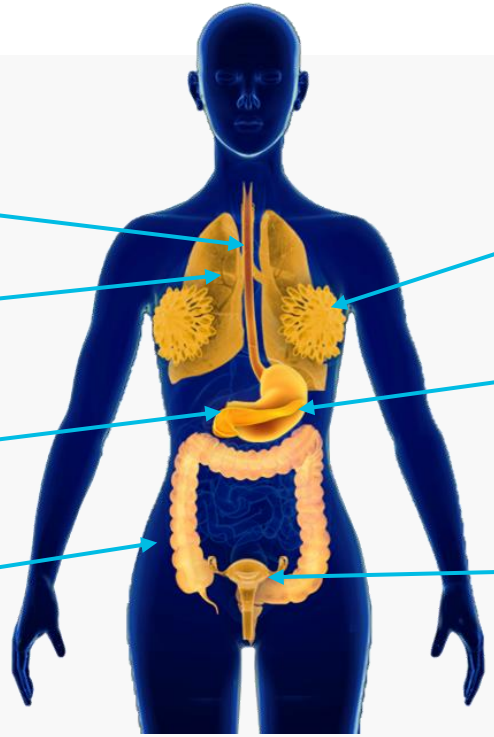
The prevalence of FGFR2b overexpression in gastric cancer (~ 30%) makes it a compelling target, and its association with poorly differentiated and diffuse type histology contributes to lower overall survival [1-3]

*Data from a randomized, double-blind, placebo-controlled, phase 2 study with a protocol allowing FGFR2b analyses on both fresh and archival samples (a majority of analyses were performed on fresh samples). [1] †Diffuse-type histology defined per Lauren classification. [2] ‡H-score is the sum of the percentage of stained tumor cells multiplied by an ordinal value corresponding to the intensity (0 = none, 1 = 1+, 2 = 2+, and 3 = 3+) and ranges from 0 to 300. [2]

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry.

1. Catenacci D, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; May 20, 2021; Online Virtual Scientific Program. Abstract 4010. **2.** Ahn S, et al. *Mod Pathol.* 2016;29:1095-1103. **3.** Ishiwata T. *Front Biosci (Landmark Ed).* 2018;23:626-639.

The FGFR2b Protein Is Expressed in Various Tumors [1,2]



- Esophageal cancer [1]
- Lung cancer [1]
- Pancreatic cancer [1]
- Colorectal cancer [1]
- Breast cancer [1]
- Gastric/gastroesophageal junction cancer [2]
- Gynecological cancers:
  - Uterine cervical [1]
  - Endometrial [1]
  - Ovarian cancer [1]

FGFR2b expression levels reported in the literature are limited and employ varying testing methodologies and scoring algorithms to define FGFR2b positivity.

Clinically meaningful expression rates of FGFR2b across tumor types, disease stages, and lines of therapy may vary and are an area of active investigational interest [1,2]

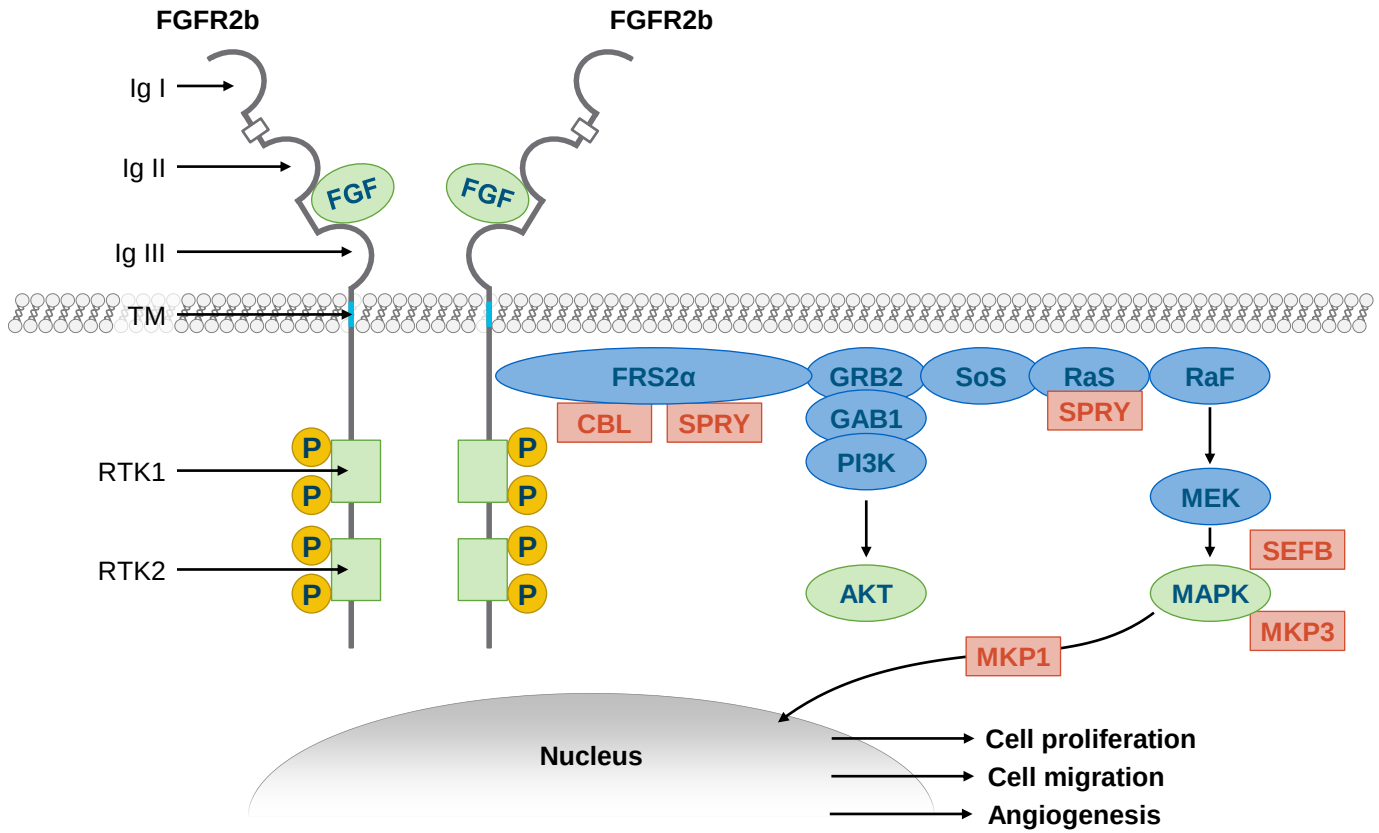
FGFR2b, fibroblast growth factor receptor 2, isoform IIIb.

1. Ishiwata T. *Front Biosci (Landmark Ed).* 2018;23:626-639. **2.** Wainberg ZA, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; January 15–17, 2021; Online Virtual Scientific Program. Abstract LBA160.

The FGFR2b Protein Is a Receptor Tyrosine Kinase Involved in Numerous Cellular Functions [1]

- FGFR2b is one of the proteins resulting from the transcription and subsequent translation of the *FGFR2* gene [2]
- FGFR2b is primarily expressed in epithelial cells [2]
  - Due to its unique extracellular domain, only a specific subset of FGF ligands will bind to the receptor
- Ligand binding and homodimerization activate downstream signaling pathways, including the PI3K-AKT and RAS-MAPK pathways, that function in cell proliferation, migration, and angiogenesis [3]

FGFR2b Drives Multiple Cellular Functions [1,4]

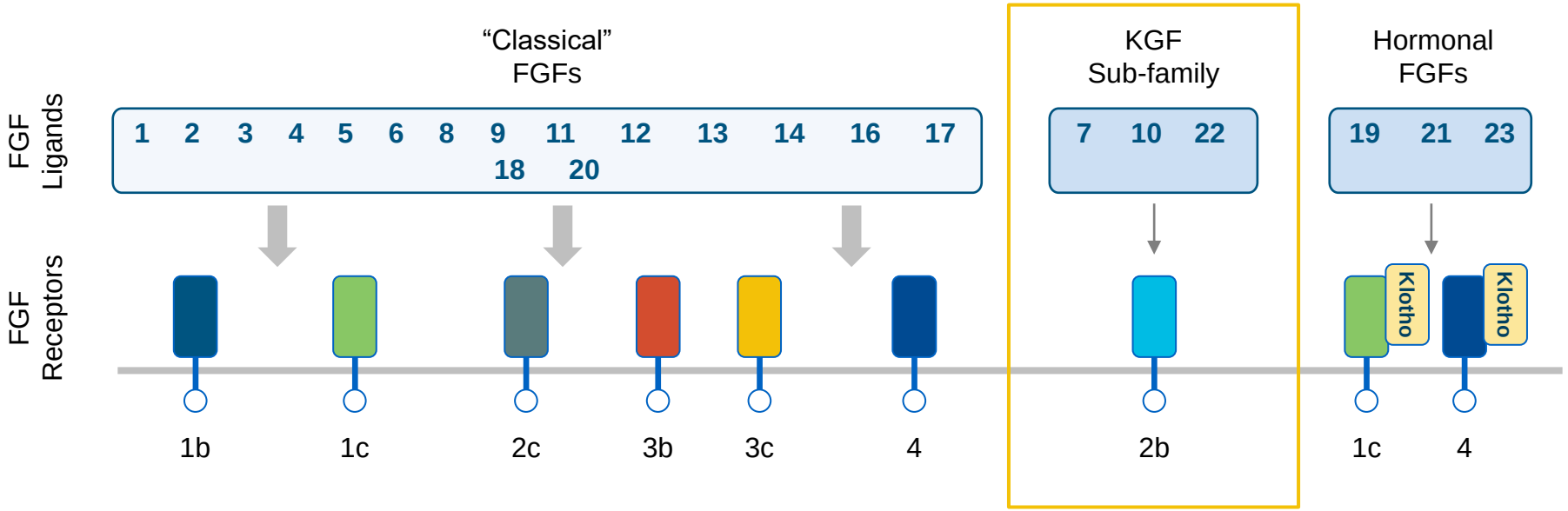


AKT, protein kinase B; CBL, Casitas B lineage lymphoma; FGF, fibroblast growth factor; FGFRL1, FGF receptor-like 1; FGFR2, FGF receptor 2; FGFR2b, FGFR2, isoform IIIb; FRS2α, FGFR substrate 2α; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound 2; Ig, immunoglobin; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MKP1, mitogen-activated protein kinase phosphatase 1; MKP3, mitogen-activated protein kinase phosphatase 3; P, phosphate; PI3K, phosphoinositide 3-kinase; RaF, proto-oncogene, serine/threonine kinase; RAS, rat sarcoma; RTK, receptor tyrosine kinase; SAM, S-adenosyl methionine; SEF, similar expression to *FGF* genes; SEFB, SAM-dependent methyltransferase; SoS, son of sevenless; SPRY, sprouty protein; TM, transmembrane.

1. Turner N, et al. *Nat Rev Cancer*. 2010;10:116-120. **2.** Ishiwata T. *Front Biosci*. 2018;23:626-639. **3.** Del Piccolo N, et al. *J Biol Chem*. 2017;292(4):1288-1301. **4.** Khosravi F, et al. *Front Cell Dev Biol*. 2021;9:672935. doi:10.3389/fcell.2021.672935.

A Unique Subset of FGF Ligands Bind With High Specificity to FGFR2b [1]

Specificity of the FGF Family of Ligands for Different FGF Receptors [1]



- Pan-FGFR inhibitors can disrupt multiple ligand-receptor interactions with undesirable side effects (eg, hyperphosphatemia may occur with the disruption of FGF23-FGFR binding) [2,3]

Specifically targeting the FGFR2b protein presents an opportunity to interrupt cancer cell proliferation while minimizing potential unwanted effects seen with pan-FGFR inhibitors [2,3]

FGF, fibroblast growth factor; FGFR, FGF receptor; FGFR2b, FGFR 2, isoform IIIb; KGF; keratinocyte growth factor.

1. Powers J, et al. Presented at: American Association for Cancer Research 10th Annual Meeting; April 16–20, 2016; New Orleans, LA. Abstract 1636. **2.** Kommalapati A, et al. *Cancers.* 2021;13:1-18. **3.** Catenacci DVT, et al. *J Clin Oncol*. 2020;38:2418-2426.

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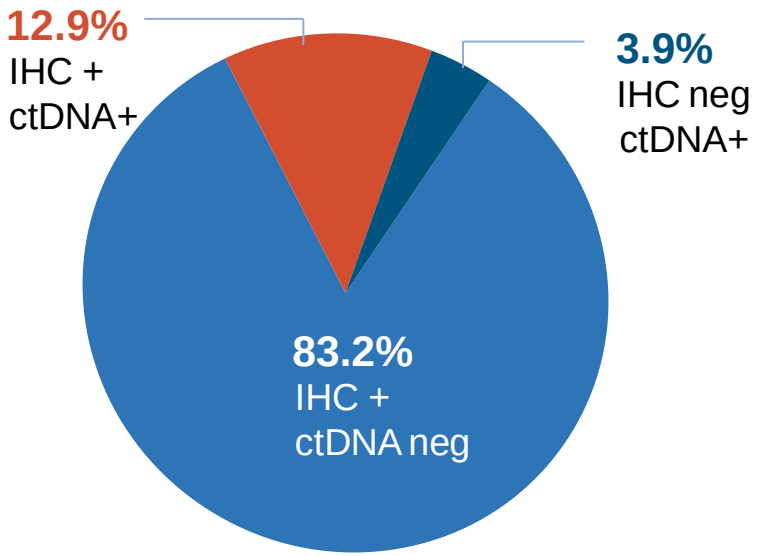
FGFR2b Protein Overexpression and *FGFR2* Gene Amplification Are Distinct [1]

- **Gene amplification** is an increase in the copy of a specific gene, which may lead to protein overexpression [2]
- **Protein overexpression** is the overabundance of a specific protein [3]
- In addition to gene amplification, other biological processes (eg, dysregulated protein synthesis and degradation) can result in protein overexpression [4]

FGFR2/FGFR2b Status of Patients with G/GEJ cancer [1,*]



IHC = FGFR2b protein expression; ctDNA = *FGFR2* gene amplification

FGFR2b protein overexpression may occur in the absence of *FGFR2* gene amplification (measured using ctDNA), thus it is important to test for FGFR2b protein overexpression using IHC [1]

*Data from a randomized, double-blind, placebo-controlled, phase 2 study of patients with metastatic gastric cancer. [1]

ctDNA, circulating tumor DNA; FGFR2, FGF receptor 2; FGFR2b, FGFR2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry.

1. Wainberg ZA, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; January 15–17, 2021; Online Virtual Scientific Program. Abstract LBA160. **2.** National Cancer Institute. www.cancer.gov. Accessed November 18, 2021. **3.** Bolognesi B, et al. eLIFE. 2018;7:e39804. **4.** Du Z, et al. *Mol Cancer*. 2018;17:58.

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Biomarker Testing Considerations for Patients With Gastric Cancer

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FGFR2b Protein Expression Can Be Assessed Using IHC, a Well-Established Methodology [1,2]

Key Features of Using IHC for Biomarker Detection of Tissue Biopsies *

Convenient [3,4]	Turnaround Time [4,5]	High Sensitivity [6]	High Specificity [5,7]	Inexpensive [4,7]
Commonly used as part of diagnostic workflows to assess biomarkers (eg, *HER2*, PD-L1)	Fast (typically 1-4 days) due to widely available methodology	IHC provides diagnostic guidance with high sensitivity (up to 100%)†	Overall optimal specificity with high concordance across assay types (eg, 97%‡)	Costs may vary due to additional biopsy collection

Optimizing workflows can help ensure adequate tissue is available to perform all diagnostic testing needed [8]

*Cytological specimens that contain circulating tumor cells can be used to test for and detect molecular biomarkers in patients with metastatic disease. [9] †Sensitivity of IHC assays depend on pretreatment conditions, antibody clones, and signal detection systems. [10] ‡Concordance between 22C3 and 28-8 pharmDx assays was 97% in 3,050 matched samples with PD-L1 expression data for both assays. [5]

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1.

1. Catenacci DVT, et al. *Future Oncol.* 2019;15:2073-2082. **2.** Wu C, et al. *Clin Biochem.* 2020;84:1-12. **3.** Ye DM, et al. *Oncol Lett*. 2020;19:17-29. **4.** Oncology PRO. www.oncologypro.esmo.org. Accessed January 5, 2022. **5.** Krigsfeld GS, et al. *J Clin Pathol*. 2020;73:656-664. **6.** Sukswai N, et al. *Curr Hematol Malig Rep*. 2019. doi:10.1007/s11899-019-00533-9. **7.** Aggarwal C, et al. *Nat Rev Clin Oncol*. 2020;18:56-62. **8.** Aisner D, et al. *Arch Pathol Lab Med.* 2016;140:1206-1220. **9**. Matsuoka T, et al. *World J Gastroeneterol.* 2018;24:2818-2832. **10.** Nitta H, et al. *Pathol Int.* 2016;66:313-324.

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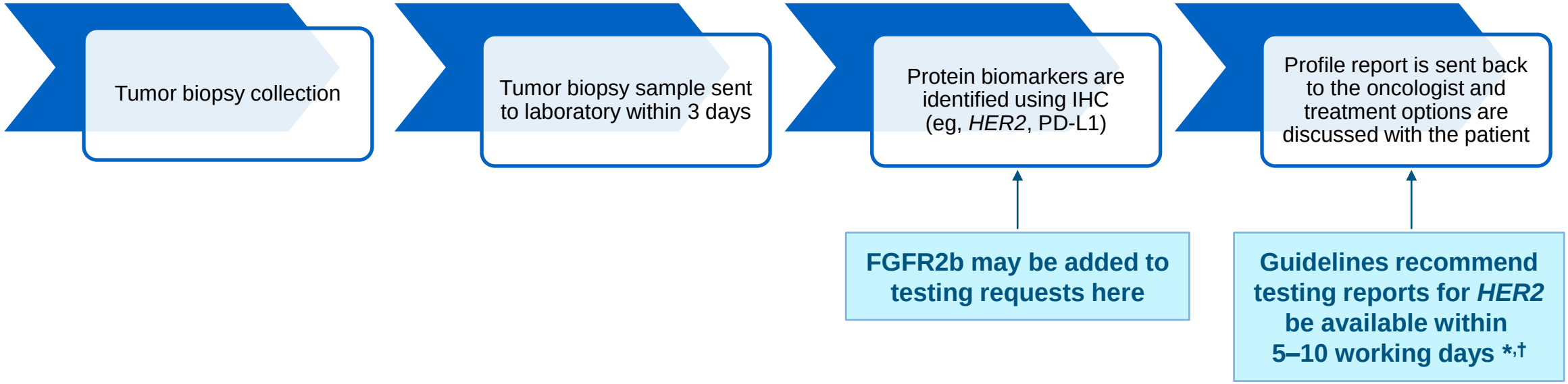
Existing Workflows for Biomarker Testing May Allow for Seamless Integration of FGFR2b Testing [1,2]

Biomarker Testing Workflow [1-7]



Integration of FGFR2b biomarker testing using IHC at diagnosis of advanced gastric cancer into existing workflows may allow for the identification of patients that are eligible for targeted therapy [1,2]

*The College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology Expert Panel recommend a benchmark of 90% of IHC or ISH reports be available within 10 working days from the date of procedure or specimen acquisition. [6] †The European Society of Medical Oncology recommends turnaround time from initial diagnosis to reporting of results should ideally not exceed 5 working days. [7]

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PD-L1, programmed cell death ligand 1.

1. Ye DM, et al. *Oncol Lett.* 2020;19:17-29. **2.** Catenacci DVT, et al. *Future Oncol.* 2019;15:2073-2082. **3.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301. **4.** Levy BP, et al. *Oncologist*. 2015;20:1175-1181. **5.** van der Velden DL, et al. *Ann Oncol*. 2017;28:3070-3075. **6.** Bartley AN, et al. *J Clin Oncol.* 2017;35:446-464. **7.** Viale G. European Society of Medical Oncology Biomarker Factsheet. Accessed February 25, 2022.

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Considerations for Biomarker Testing in Patients With Gastric Cancer

Optimizing Tissue Acquisition

- Effective communication between tissue acquirers and pathologists ensures sufficient tissue quantity and quality for biomarker testing [1]
- Tissue acquisition procedures for biomarker testing should minimize risk to the patient while ensuring adequate tissue yield [1]

Preparing and Reporting Test Results

- Pathologists and oncologists can support the development of reflex testing protocols to:
  - decrease time to biomarker identification [2]
  - reduce turnaround time [2]
- Maintaining test results in patient's electronic health record can allow easier access to providers [1]

Staying Current With Rapidly Evolving Practice Standards

- Consider multidisciplinary tumor boards and other formal venues to educate on:
  - effective biomarker testing strategies [1,3,4]
  - targeted therapy approvals [1,3]
  - evolving guidelines [1]

1. Levy BP, et al. *Oncologist*. 2015;20:1175-1181. **2.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301. **3.** van der Velden DL, et al. *Ann Oncol*. 2017;28:3070-3075. **4.** Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342.

Summary

1. Gastric cancer is a complex and heterogenous disease with a need for novel targeted treatment options [1]
2. FGFR2b protein overexpression is seen in various cancer cells, making it a compelling therapeutic target [2]
3. FGFR2b is a member of the FGFR family of receptor tyrosine kinases, and its ligands bind with high specificity to FGFR2b [3]
4. Standardization of biomarker testing may allow for integration of FGFR2b biomarker testing using IHC into future pathological testing workflows [4,5]

FGFR, fibroblast growth factor receptor; FGFR2b, FGFR 2, isoform IIIb; IHC, immunohistochemistry.

1. De Mello RA, et al. *Am Soc Clin Oncol Educ Book.* 2018;38:249-261. **2.** Ishiwata T. *Front Biosci (Landmark Ed).* 2018;23:626-639. **3.** Han N, et al. *Pathobiology*. 2015;82:269-279. **4.** Ye DM, et al. *Oncology Letters.* 2020;19:17-29. **5.** Catenacci DVT, et al. *Future Oncol.* 2019;15:2073-2082.