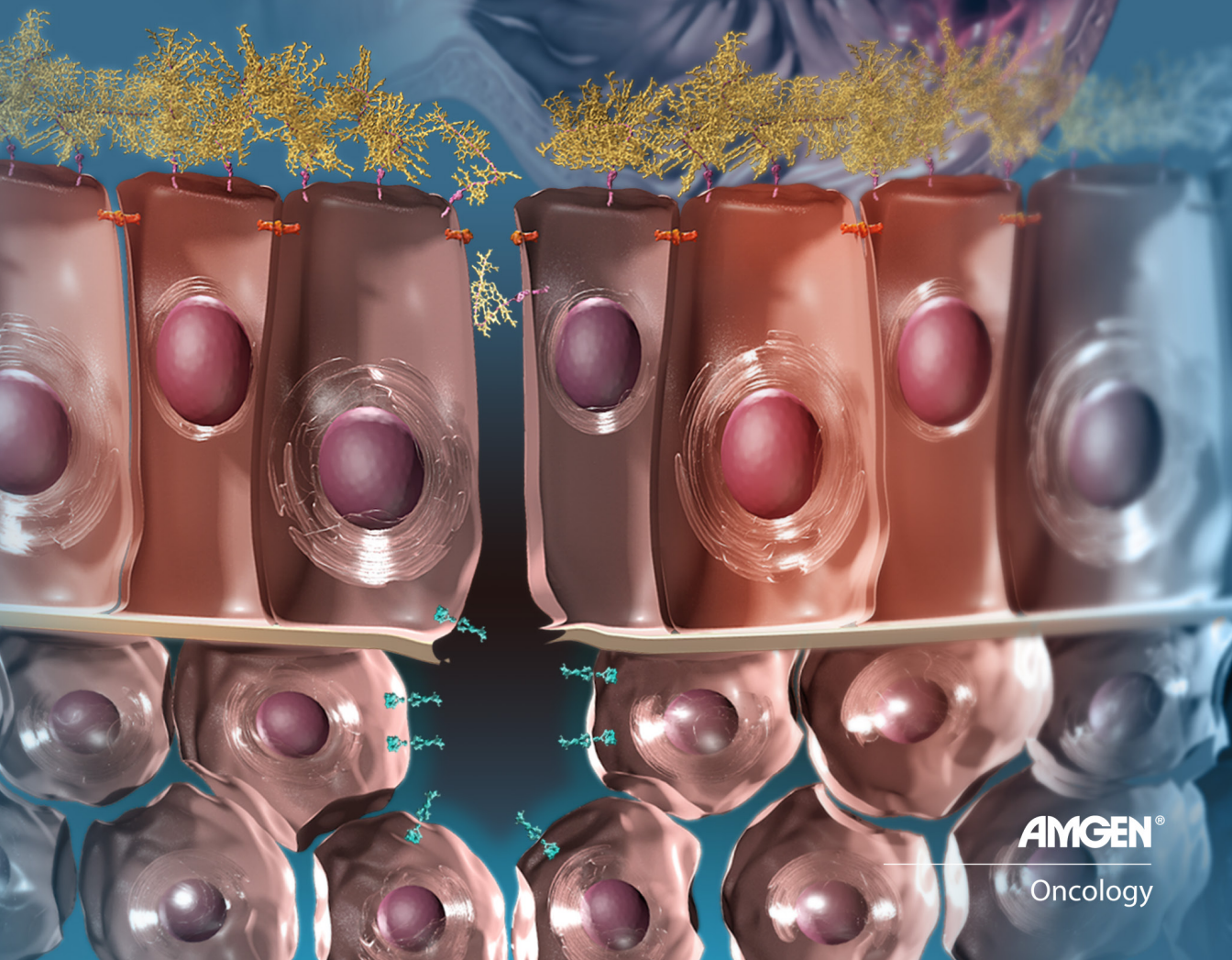


FGFR2b, MUC17, AND CLDN18.2 AS POTENTIAL THERAPEUTIC TARGETS IN GASTRIC CANCER



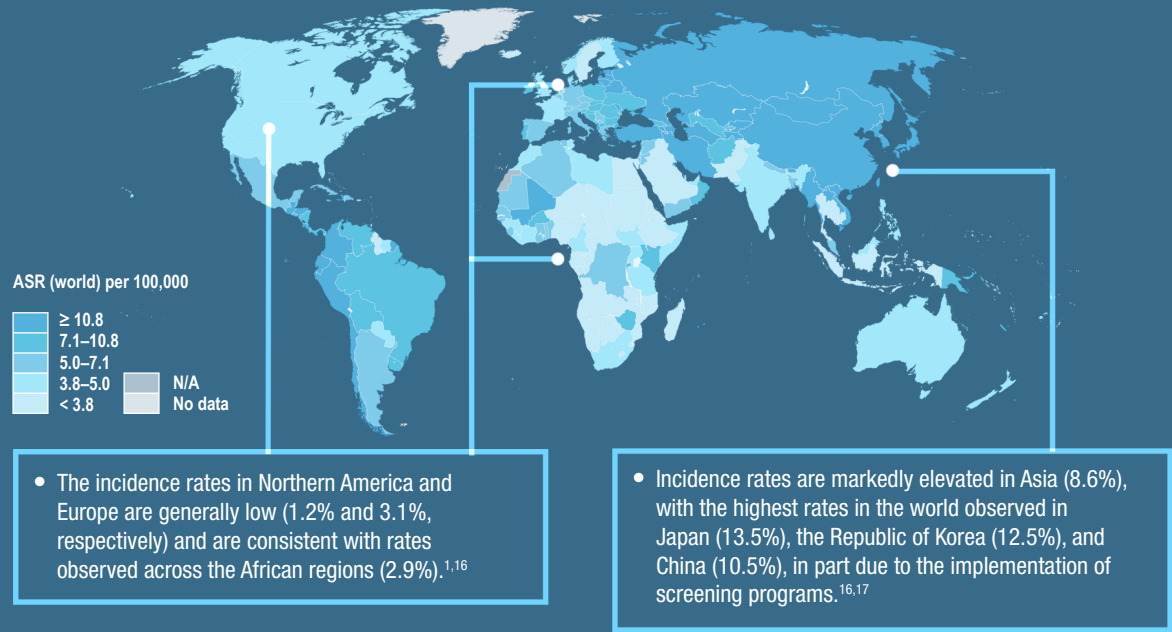
GASTRIC CANCER IS ONE OF THE MOST COMMON MALIGNANCIES, WITH VARYING INCIDENCE RATES AMONG REGIONS¹⁻⁵

Worldwide, there are over one million new cases of gastric cancer diagnosed each year, accounting for 5.7% of all new cancer diagnoses.^{1,2,*}

- Gastric cancer is the fifth most frequently diagnosed cancer, and incidence rates vary by region.^{1,2}
 - In 2021, an estimated 26,560 people will be diagnosed with gastric cancer in the United States alone.⁶
- Gastric cancer is more prevalent in males than females, and in developed countries, males are 2.2 times more likely to be diagnosed than females.^{1,2}
- Although steady decreases in the incidence of gastric cancer have been noted globally, incidence rates in specific subpopulations have increased over the past decades.^{2,3,7,8}
- Gastric cancer is a heterogenous disease characterized by the expression of certain proteins, including MUC17 and CLDN18.2, receptor tyrosine kinases (eg, FGFR2b and HER2), and growth factors (eg, VEGF).⁹⁻¹¹

In countries where gastric cancer is more common, screening programs have aided in diagnosing more cases during the disease’s early stages.^{12,13} However, screening programs are available only in a limited number of countries.^{2,14}

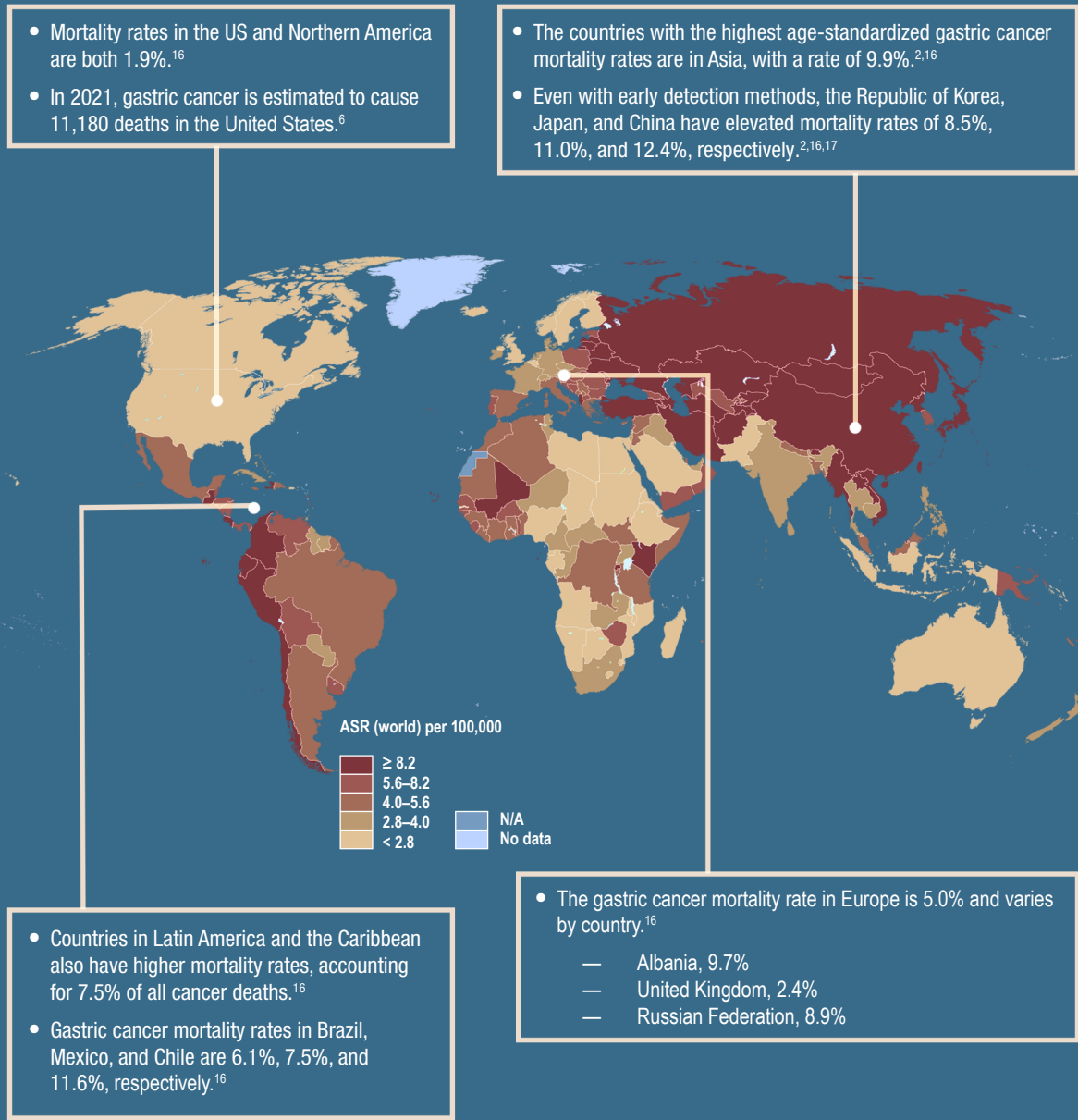
Estimated Age-Standardized Incidence Rates (World) for Gastric Cancer in 2020, Both Sexes, All Ages¹⁵



GASTRIC CANCER IS THE FOURTH LEADING CAUSE OF CANCER DEATH WORLDWIDE¹

In 2020, there were an estimated 769,000 deaths from gastric cancer, making it the fourth leading cause of cancer death in the world, with highest mortality rates observed in patients from Eastern Asia.¹

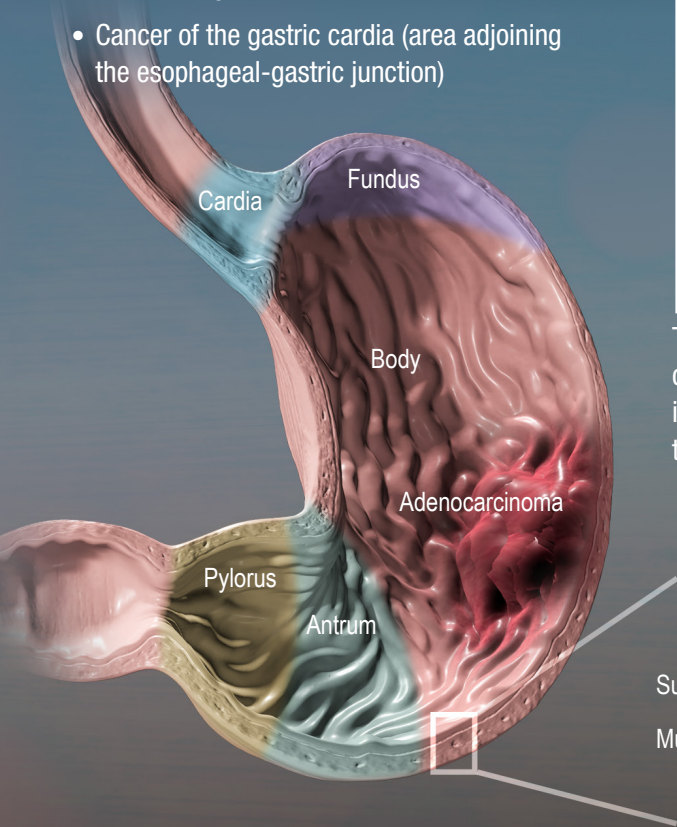
Estimated Age-Standardized Mortality Rates (World) for Gastric Cancer in 2020, Both Sexes, All Ages¹⁵



PATHOPHYSIOLOGY OF GASTRIC CANCER

Most gastric cancers (~95%) are adenocarcinomas, originating in the columnar epithelial cells in the stomach.^{18,19} Gastric cancers can generally be classified into two topographical categories:^{1,2,12,19-21}

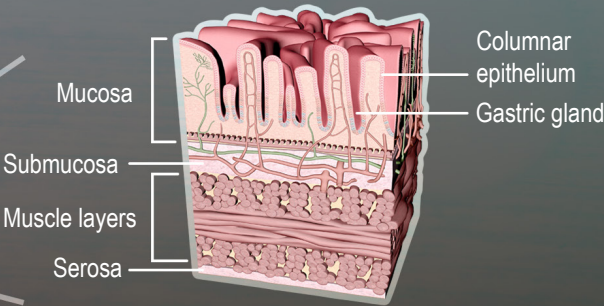
- Noncardia gastric cancer
- Cancer of the gastric cardia (area adjoining the esophageal-gastric junction)



Adenocarcinomas are histologically classified as:^{2,22}

Adenocarcinoma Classification	Frequency (%)
Intestinal or well differentiated	85–90
Diffuse or undifferentiated	10–15
Sporadic	90–95
Familial predisposition	5–10

The columnar epithelium and gastric glands composing the mucosa are prone to inflammation, known as gastritis, which can lead to peptic ulcers and, ultimately, gastric cancer.^{2,19,23}



Factors Increasing the Risk of Gastric Cancer

The development of gastric cancer is a complex, multistep process that involves environmental and genetic factors.^{13,18}

The main risk factor is *Helicobacter pylori* infection, with almost 90% of new cases of noncardia gastric cancer attributed to this bacterium.^{1,2} Other risk factors include:^{2,12,13,24}

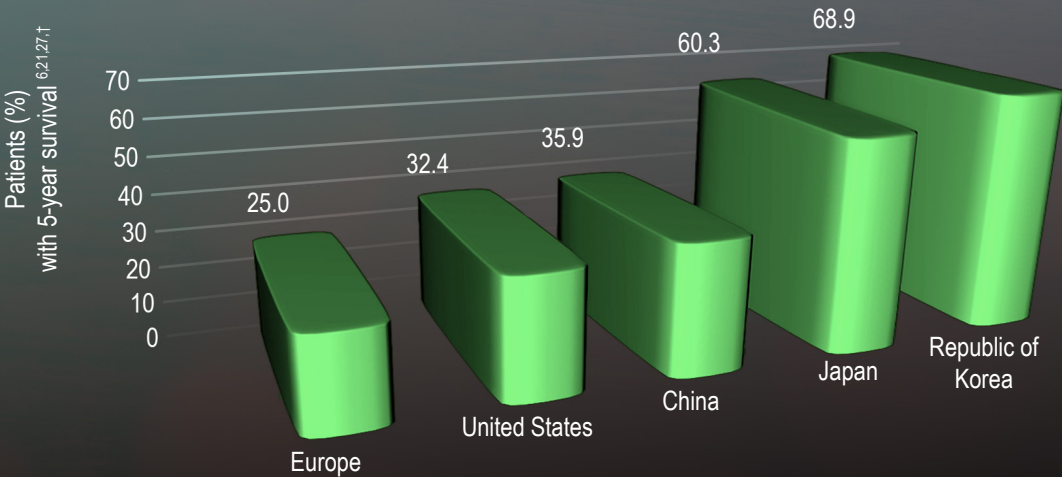
- Age
- Epstein–Barr virus
- Alcohol consumption and tobacco smoking
- Diets rich in preserved foods and salt
- Genetic risk factors such as:^{2,22,25}
 - Mutations in *CDH1*, *APC*, *EPCAM*
 - Expression of PD-L1 and high MSI

MOST PATIENTS WITH GASTRIC CANCER ARE DIAGNOSED AT AN ADVANCED STAGE, OFTEN WITH POOR PROGNOSIS AND LOW SURVIVAL RATES^{7,22,26}

Globally, patients with gastric cancer have a 5-year survival rate of ~ 20%.^{7,†} Treatment remains challenging, as many patients are diagnosed at an advanced stage and availability of targeted, personalized treatment strategies is limited.²²

The 5-year overall survival duration for patients with metastatic gastric cancer may range from 3 months with only supportive care to 16 months in fit patients enrolled in clinical trials.²²

- The Europe-wide 5-year relative survival rate from 1999–2007 was 25%.²¹
 - Southern Europe reported the greatest 5-year survival outcomes (30%)
 - Eastern Europe reported the poorest survival outcomes (19%)
- In the United States from 2011 to 2017 the 5-year survival rate was 32.4% for all stages and 5.5% for patients with metastasized cancer.⁶
- The 5-year survival rates in Japan and the Republic of Korea are notably higher due to the early detection screenings that have led to the effective diagnosis of tumors at early stages.^{7,17,27}



Patients receiving standard therapeutic regimens exhibit modest survival benefits, usually of less than 12 months.²⁶ Therapies that target tumor-associated antigens have been incorporated into these therapy regimens.^{22,28} However, the role of targeted therapies is limited in patients with advanced-stage gastric cancer, representing an unmet medical need.²²

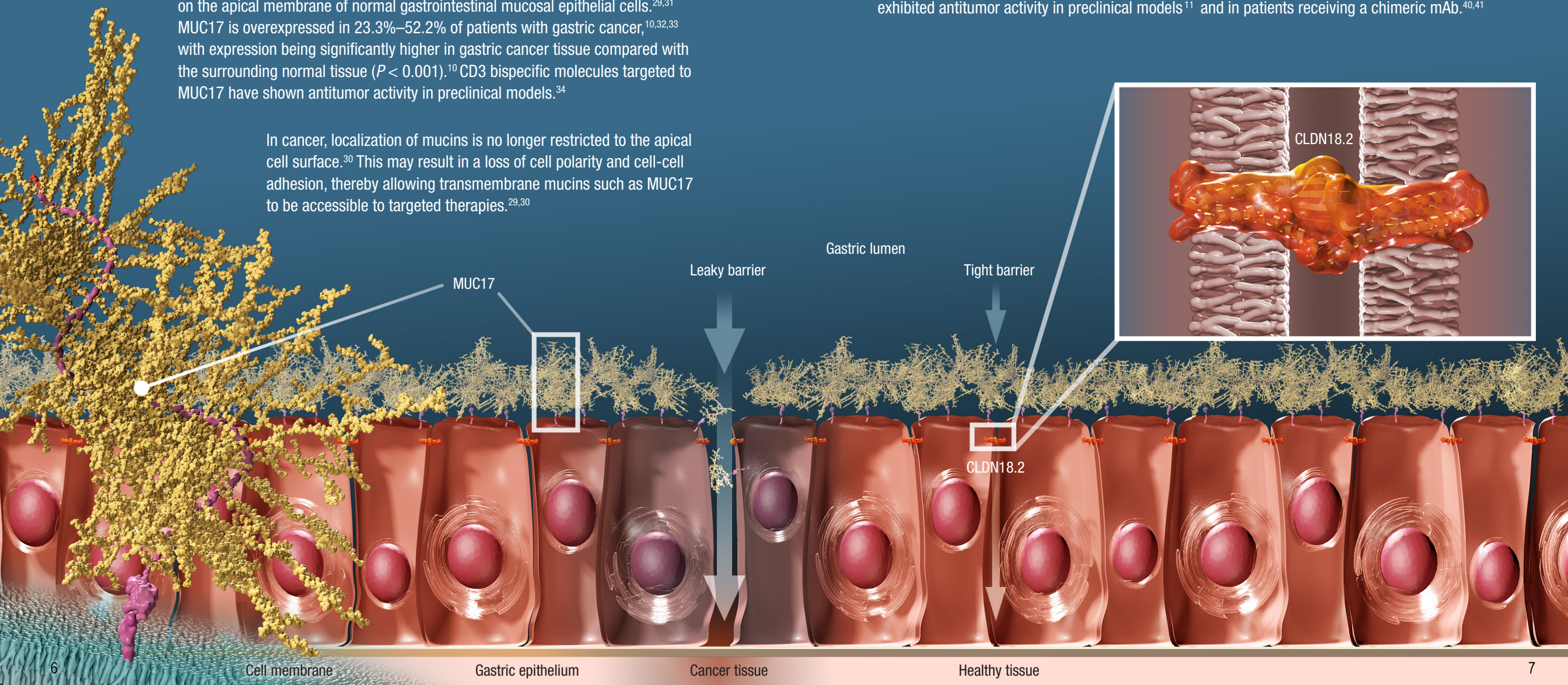
[†]Data from 195 countries and territories from 21 regions between 1990 and 2017.⁷
[†]Data collection for the US was from 2011 to 2017; China, Japan, and Republic of Korea from 2010 to 2014; Europe from 1999 to 2007.²⁷

MUC17 IS HIGHLY EXPRESSED IN GASTRIC CANCER AND REPRESENTS A POTENTIAL THERAPEUTIC TARGET^{10,29-33}

One of the primary components of the mucosal barrier that protects the underlying stomach epithelium is the mucin family of glycosylated proteins.²⁹ Mucins are often overexpressed in cancer and have been found to be both therapeutic targets and biomarkers predicting the prognosis of various cancers.^{29,30}

MUC17, a member of the mucin family, is a transmembrane protein expressed on the apical membrane of normal gastrointestinal mucosal epithelial cells.^{29,31} MUC17 is overexpressed in 23.3%–52.2% of patients with gastric cancer,^{10,32,33} with expression being significantly higher in gastric cancer tissue compared with the surrounding normal tissue ($P < 0.001$).¹⁰ CD3 bispecific molecules targeted to MUC17 have shown antitumor activity in preclinical models.³⁴

In cancer, localization of mucins is no longer restricted to the apical cell surface.³⁰ This may result in a loss of cell polarity and cell-cell adhesion, thereby allowing transmembrane mucins such as MUC17 to be accessible to targeted therapies.^{29,30}



THE TIGHT JUNCTION MOLECULE CLDN18.2 IS A POTENTIAL THERAPEUTIC TARGET FOR GASTRIC CANCER^{11,35-41}

Claudins are a family of tight junction proteins establishing paracellular barriers which control flow of molecules between cells.³⁵ CLDN18.2 (tight junction molecule claudin-18 isoform 2) is highly expressed in the healthy stomach and is strictly confined to differentiated epithelial cells of the gastric mucosa.¹¹ CLDN18.2 is also expressed in 14.1%–87% of primary gastric cancers.³⁶⁻³⁹

CLDN18.2-specific antibodies and CD3 bispecific molecules developed to target CLDN18.2 have exhibited antitumor activity in preclinical models¹¹ and in patients receiving a chimeric mAb.^{40,41}

FGFR2B OVEREXPRESSION IN GASTRIC AND GEJ CANCERS PRESENTS A PROMISING TARGET⁴²⁻⁵³

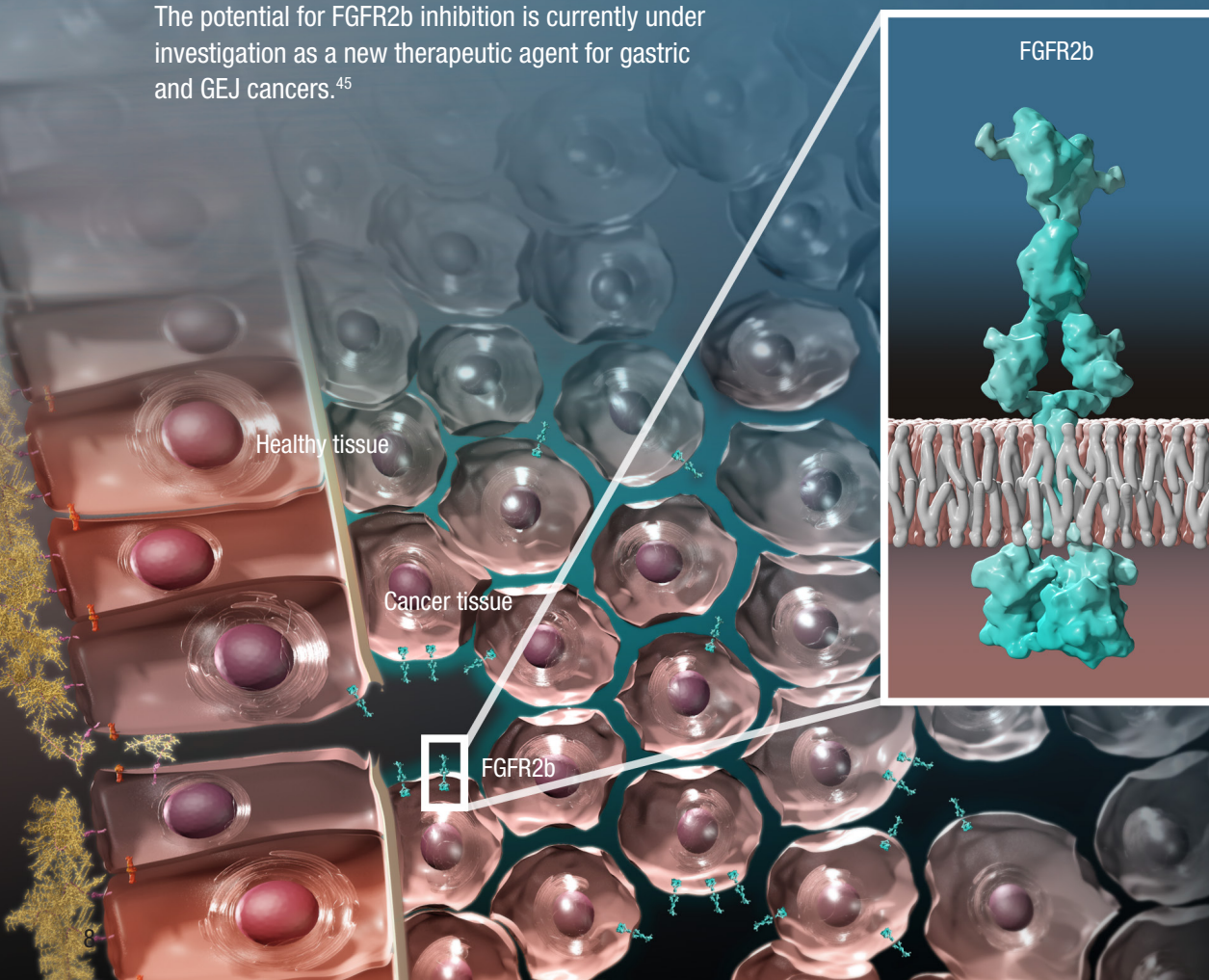
Fibroblast growth factor receptor 2b (FGFR2b) is a transmembrane receptor tyrosine kinase (RTK) that participates in tissue repair, wound healing, and angiogenesis.⁴²

FGFR2b is an isoform of the FGFR2 gene and belongs to the FGFR family of receptor tyrosine kinases.⁴³

FGFR2b is overexpressed in a subset of gastric and gastroesophageal junction (GEJ) cancers, including those tumors where the FGFR2 gene is amplified. Overexpression of FGFR2b on the basal surface of gastric epithelia is observed in 3%–61% of gastric and GEJ cancers, depending on tumor stage and detection assay.⁴⁴⁻⁴⁶ In tumors with FGFR2 amplification, it is the FGFR2b splice variant that is almost invariably expressed on the cell surface.⁴⁷⁻⁴⁹

FGFR2b has been detected in other cancers, including pancreatic, uterine, cervical, lung, and colorectal cancers.⁵⁰⁻⁵⁴

The potential for FGFR2b inhibition is currently under investigation as a new therapeutic agent for gastric and GEJ cancers.⁴⁵



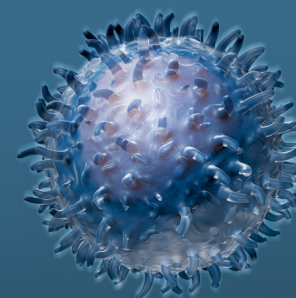
A NUMBER OF MODALITIES ARE BEING INVESTIGATED TO TARGET GASTRIC CANCER^{11,40,41,55-65}

Several therapeutic candidates are currently being investigated in patients with gastric cancer, using several different modalities that target tumor-associated antigens.^{11,40,41,55-65}



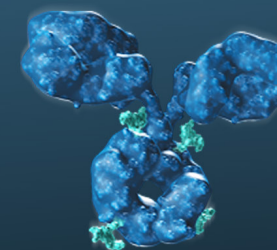
BiTE[®] molecule

- **Bispecific molecules**—including BiTE[®] (Bispecific T-cell Engager) molecules—simultaneously bind a tumor-associated antigen and a T-cell antigen (such as CD3), which redirects T cells to kill tumor cells.¹¹
 - BiTE[®] molecules that target MUC17 or CLDN18.2 are under investigation for gastric cancer therapy.^{11,34,57}



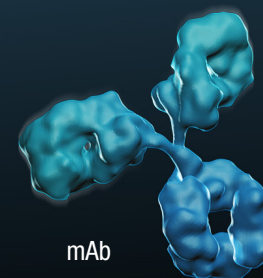
CAR T cell

- **CAR-T therapy**: designed to use T cells isolated from the patient that have been engineered to target one or multiple antigens and promote tumor inhibition.^{58,59}



ADC

- **Antibody-drug conjugates (ADCs)**: these drugs combine a tumor-antigen-specific mAb with a cytotoxic drug and exert cytotoxic effects upon binding.^{60,61}
- Monoclonal antibodies that specifically bind to targets in gastric cancer can be used to inhibit tumor growth and kill cancer cells by indirect (complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity) and direct (antiproliferative and proapoptotic effects) mechanisms.^{40,41,62} mAbs often target RTKs or immune checkpoints.⁶²⁻⁶⁵



mAb

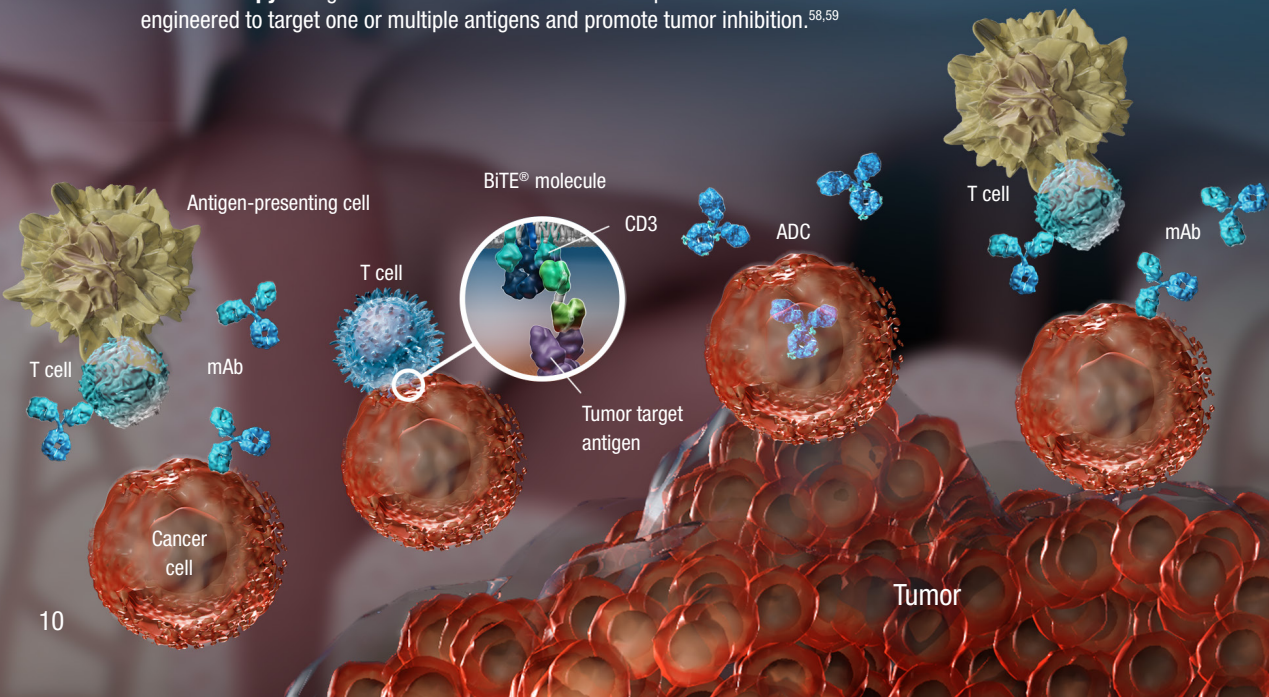
- RTKs are often involved in the proliferation, differentiation, and migration/invasion of gastric cancer cells.⁶²⁻⁶⁴
- Immune checkpoint inhibitors, such as those targeting PD-1 and CTLA-4, prevent the induction of immunotolerance to the tumor by activating cytotoxic T cells.⁶²⁻⁶⁵
- mAbs such as those that target FGFR2b are under investigation for the treatment of gastric cancer.⁴⁵

KEY TAKEAWAYS

- Gastric cancer is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer death in the world.^{1,2} The incidence and mortality rates vary by region, with incidence rates increasing in some subpopulations.¹⁻⁵
- Gastric cancer develops via a complex, multistep process, and is often diagnosed at an advanced stage, with limited available treatments resulting in poor patient outcomes.^{7,13,18,22,26}
- Gastric cancer is a heterogenous disease characterized by the overexpression and mis-localization of certain proteins, including MUC17, CLDN18.2, and RTKs (eg, FGFR2b, HER2), and growth factors (eg, VEGF).⁹⁻¹¹
- Disruptions to molecules in the stomach epithelium occur during gastric cancer,^{29,30,40} which result in high expression of MUC17^{29,30,40} and CLDN18.2.^{11,36-39}
- The overexpression of MUC17, CLDN18.2, and FGFR2b on the surface of gastric and GEJ cancers makes them potential therapeutic targets.^{11,31,46}
- A number of modalities are being investigated to target specific tumor-associated antigens in gastric cancer, including bispecific molecules such as BiTE[®] molecules, CAR-T therapies, ADCs, and monoclonal antibodies.^{11,40,41,55-65}

Glossary:

- **Antibody-drug conjugate:** these drugs combine a tumor-antigen-specific mAb with a cytotoxic drug and exert cytotoxic effects upon binding.^{60,61}
- **Monoclonal antibody:** specifically bind targets which can be used to inhibit tumor growth and kills cancer cells through indirect and direct mechanisms.^{40,41,62}
- **BiTE[®] molecule:** Bispecific T-cell Engager molecules simultaneously bind a tumor target antigen and a T-cell antigen, which redirect T cells towards the recognition of tumor target antigen and induces T-cell-mediated cell killing.¹¹
- **CAR-T therapy:** designed to use T cells isolated from the patient that have been engineered to target one or multiple antigens and promote tumor inhibition.^{58,59}




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Abbreviations:

ADC, antibody-drug conjugate; APC, adenomatous polyposis coli; ASR, age-standardized rate; BiTE[®], Bispecific T-cell Engager; CAR, chimeric antigen receptor; CDH1, cadherin-1; CD3, cluster of differentiation; CLDN18.2, claudin-18 isoform 2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EPCAM, epithelial cell adhesion molecule; FGFR2b, fibroblast growth factor receptor 2, isoform IIb; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MSI, microsatellite instability; MUC17, mucin 17; N/A, not applicable; PD-L1, programmed death ligand 1; PD-1, programmed cell death protein 1; RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor.



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