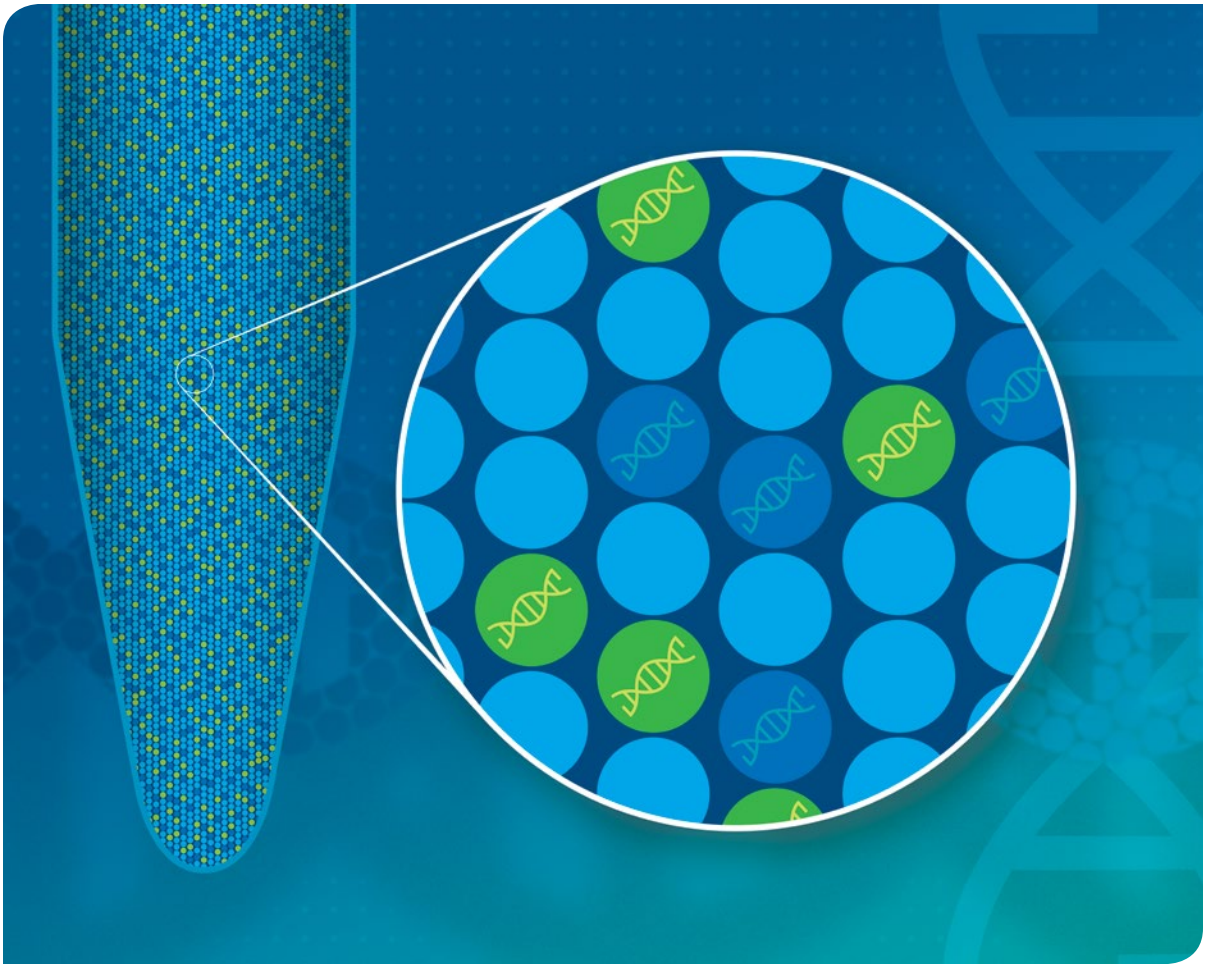


QXDx ddPCR Portfolio

Start with a droplet. End with patient management.

IVD

BIO-RAD

This droplet marks a decisive moment in his cancer recovery

As personalized treatments for cancer become more widespread, so do questions for which targeted therapy is most effective and when that therapy needs to be changed. Through the use of liquid biopsy with Droplet Digital PCR (ddPCR), clinical laboratories can now support clinicians in determining the most effective treatment based on a patient's oncogenomic profile.

Liquid biopsy, also known as plasma genotyping, is a non-invasive method used for detecting cancer cells or DNA in a patient's blood. **Droplet Digital PCR** detects low abundance mutations in complex backgrounds by partitioning a sample into thousands of separate DNA or RNA molecules within nanoliter-sized droplets. Each droplet can then be directly detected and quantified with extreme sensitivity and precision.

Combining liquid biopsy with the power of Droplet Digital PCR can provide clinicians with an efficient and economical method to diagnose, monitor and treat cancer and other conditions.

Premier Clinical-Ready QXDx ddPCR Portfolio

Same Result – Any Lab, Any Instrument, Any Operator

QXDx Automated Droplet Generator
with QXDx Droplet Reader

Discover Droplet Digital PCR

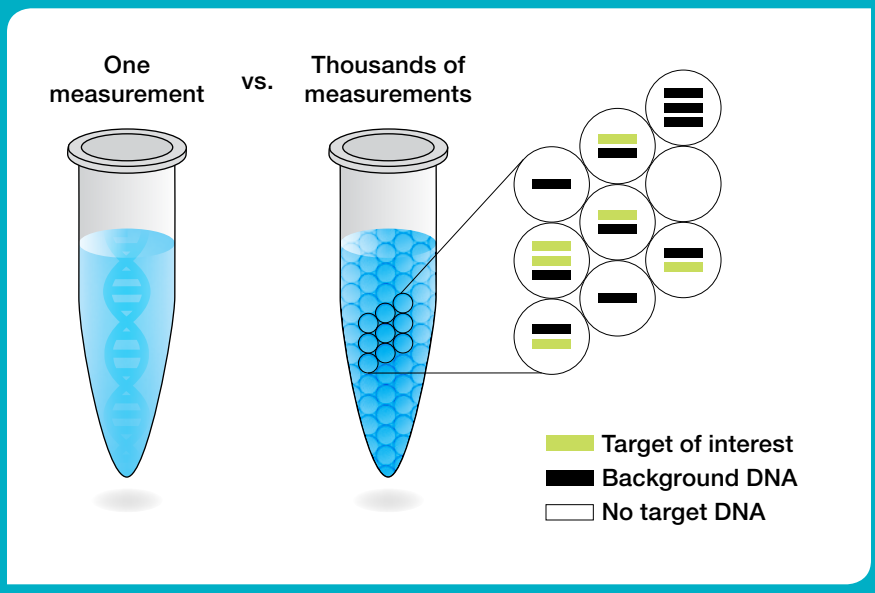
Absolute quantification of target DNA or RNA molecules with unrivaled precision, accuracy and reproducibility

Droplet Digital PCR provides highly sensitive absolute quantification of DNA or RNA in serum, plasma, tissue or urine samples along with increased precision and reproducibility, without the need for standard curves. ddPCR sample partitioning with statistical analysis of sample targets minimizes variability from common sources of error that can influence quantitative PCR results, including standard curves that cause cross-sample variation and PCR inhibitors that alter assay efficiency.

The Bio-Rad QXDx Droplet Digital PCR System utilizes a simple, user-friendly and scalable workflow to meet your throughput and sensitivity needs. The same FDA-cleared system for use with current and future cleared kits can also be leveraged with Bio-Rad's assays or you may develop and validate your own assays using the Research Use Only (RUO) separately partitioned software.

The Power of Partitioning

Sample partitioning is the key to Droplet Digital PCR. While traditional PCR provides just one PCR reaction, ddPCR uses advanced microfluidics technology to partition a single sample into 20,000 uniform nanoliter-sized droplets for thousands of PCR reactions per well. Each droplet is then analyzed for the presence of fluorescence associated with the probe detection of the target sequence.

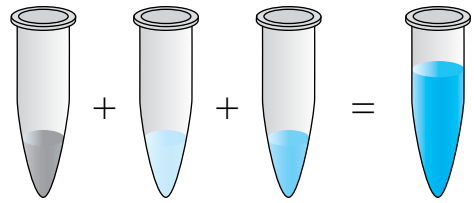


An Economical and Scalable Workflow

Enabling from 8 to 96 samples per run

1 Prepare ddPCR reaction mix

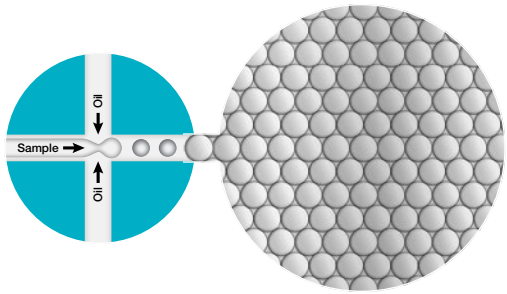
Combine DNA sample and ddPCR assay along with supermix for ddPCR reaction mixture.



DNA sample | ddPCR supermix | ddPCR assay | ddPCR reaction mix

2 Generate droplets

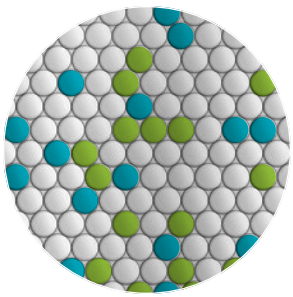
Load ddPCR reaction mix into the droplet generator.



A sample is partitioned into 20,000 droplets.

3 Perform PCR

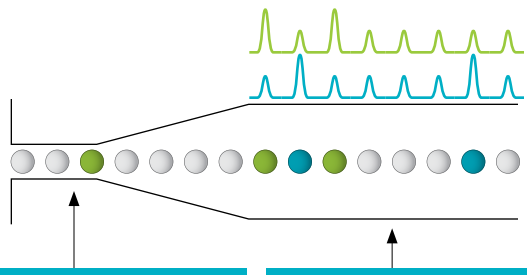
Perform PCR with a thermal cycler.



Droplets containing target DNA are now fluorescent.

4 Read and analyze results

Read samples by digitally counting positive and negative droplets. Quantitate samples by automatically applying Poisson statistics.



Droplets stream single file through a droplet reader for fluorescence analysis.

Positive droplets with >1 DNA molecule show increased fluorescence compared to negative droplets.

Droplet Digital PCR Goes Clinical

ddPCR technology has expanded beyond research and moved into clinical laboratories with applications in monitoring.

Bio-Rad's Direction with Clinical Lab Applications

- Oncology
- Reference Standards
- Newborn Screening
- Infectious Disease

A growing number of labs now leverage ddPCR for mutation detection, understanding that ddPCR might provide greater medical and economic value.

Expected Medical Impact

- Accurately monitor patient treatment progress
- Eliminate need for patient tumor biopsy (through use of liquid biopsy)

Expected Economic Impact

- Reduce unnecessary biopsy costs
- Reduce unnecessary biomarker testing (specifically with NGS)

Over 3000 ddPCR clinical research and basic research publications are available.

NIST, NMI and other global standards institutes recognize and utilize ddPCR for reference standard quantification.

Same Result, Any Lab, Any Instrument and Any Operator

Reproducibility, accuracy and precision through digital counting of copies of target molecules

Scalable Throughput and Workflow

Sensitivity scaled on replicates, 8 to 96 samples per run, and simple workfow—similar to qPCR

Absolute Quantification

Requires no standard curves, just droplet counting

A Case for Droplet Digital PCR

One in eight women in the United States will be diagnosed with breast cancer in their lifetime and approximately 41,760 American women will die of breast cancer in 2019.[1,2] Early detection of breast cancer has driven death rates to decline by 40% over the last three decades.[2]

The Challenge

As early detection of breast cancer increases it raises the next challenge of detecting microscopic metastases that can result in overt metastatic reoccurrence. The challenge for many women with breast cancer is that their cancer has metastasized at their diagnosis with undetected micrometastatic residual disease or minimal residual disease (MRD).[3] The resulting challenges clinicians face are the identification of cancer patients with MRD after intervention and early detection of molecular relapse.

Circulating Tumor DNA (ctDNA)

Liquid biopsy of the plasma or serum for detecting circulating tumor DNA (ctDNA) offers clinicians a tool to make further advances in the fight against the progression of cancer. In the effort to identify advanced cancers, the next promising step is to use ctDNA to analyze patients with early stage cancer, which requires reproducible and highly-sensitive results.

Study

Studies from Dr. Nick Turner's lab at the Breakthrough Breast Cancer Research Centre[3] assessed the potential of detecting molecular relapse well before clinical relapse is evident, by assaying for plasma ctDNA in early stage primary breast cancer patients, first in 55 patients and later in an expanded study with an additional 213 patients.[3,4] Bio-Rad's droplet digital polymerase chain reaction (ddPCR) system was used with personalized single nucleotide variation (SNV) assays based on tumor NGS genotyping to identify patients with MRD that are at risk of cancer relapse.

Conclusions

Bio-Rad's ddPCR system showed a robust ability to rapidly run ddPCR assays for diverse SNV mutations. Outcomes from the multiple studies showed:

- Molecular relapse was detected with a median time of 10.7 months prior to clinical relapse with one patient being detected roughly four years before evidence of clinical relapse.[4]
- Detection of ctDNA in a single postsurgical sample and "mutation tracking" of serial samples were significant predictors for early relapse.[3]
- Serial "mutation tracking" of extra-cranial relapse was detected with near perfect clinical sensitivity (100%, 12/12) and specificity (96%, 27/28).[3]
- Predicted relapse was shown in all major subtypes (ER+, ER-, & TNBC).
- Utilizing droplet digital PCR with Bio-Rad's QXDx AutoDG ddPCR system to assay plasma samples gives clinicians one of "the most sensitive techniques currently available for detection of known rare mutations."[3]

REFERENCES

[1] U.S. Breast Cancer Statistics (2019). https://www.breastcancer.org/symptoms/understand_bc/statistics. Last revised Feb 13, 2019. Accessed May 15, 2019.

[2] American Cancer Society (2019). Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019.

[3] Garcia-Murillas I et al. (2015). Mutation tracking in circulating tumor DNA predicts relapse in early breast cancer. Sci Transl Med. 7, 302.

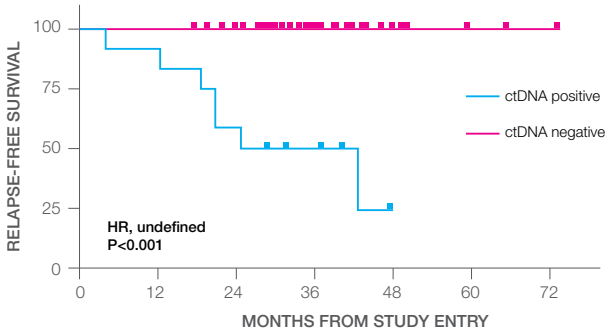
[4] Garcia-Murillas I et al. (2018). Molecular Residual Disease detection with circulating tumor DNA analysis predicts relapse in patients with early stage breast cancer. Poster session presented at the San Antonio Breast Cancer Symposium, San Antonio.

Serial Monitoring of ctDNA for Breast Cancer Subtypes on ddPCR

A multicenter study for detecting ctDNA after treatment of early stage breast cancer using the complementary technologies, NGS and ddPCR, to predict molecular relapse.

ER+ (N=51)

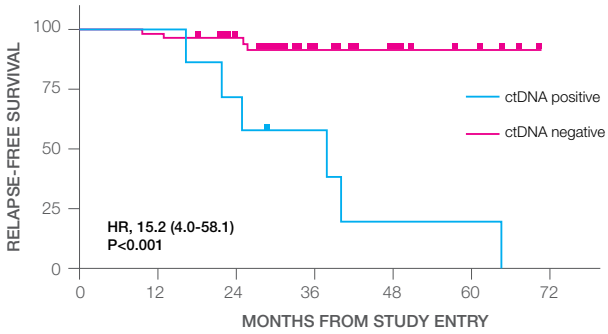
No patients relapsed in the ctDNA negative group (Hazard Ratio (HR) not definable).



NUMBER AT RISK								
	ctDNA positive	12	11	7	4	0	0	0
	ctDNA negative	39	39	34	20	6	3	1

HER2+ (N=55)

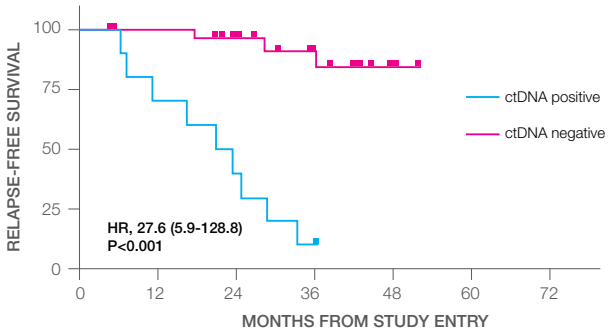
Showed HR = 15.2 with a median lead time of 14.5 months over clinical relapse.



NUMBER AT RISK								
	ctDNA positive	7	7	5	3	1	1	0
	ctDNA negative	48	47	39	19	9	4	0

TNBC (Triple Negative Breast Cancer) (N=38)

Showed HR = 27.6 with a median lead time of 10.6 months.[4]



NUMBER AT RISK								
	ctDNA positive	10	7	4	0	0	0	0
	ctDNA negative	28	26	20	12	3	0	0

The data above is from the 2018 SABCS multi-center trial[4] and is consistent with the original proof of principle study.

Precision Medicine Workflow

QXDx BCR-ABL %IS Kit

For monitoring CML patients

The QXDx BCR-ABL %IS Kit elevates chronic myeloid leukemia (CML) monitoring to a new level of precision, reproducibility, and sensitivity (0.0028%IS, MR 4.56). Assess Complete Molecular Response with this highly sensitive molecular assay. Directly report standardized results with International Scale (%IS) and Molecular Response (MR) values.

IVD

Bio-Rad's first IVD test kit for Droplet Digital PCR

Customer Testimonial

"Bio-Rad's Droplet Digital PCR platform increases the sensitivity and precision of BCR-ABL1 measurements as compared to qPCR. Along with absolute quantification without standard curves (in copies), the system is ideal for use in routine laboratory testing."

– Niels Pallisgaard, Head of Molecular Pathology, Zealand University Hospital

QXDx Universal Kits

(General Purpose Reagents)

Bio-Rad's GMP-manufactured, general purpose reagents, for any routine ddPCR workflow, are designed to drive efficiency in consumption and ordering. Kits consist of 3 packs – Consumable Pack, Oil Pack and Supermix Pack – for use on the QXDx AutoDG ddPCR systems.

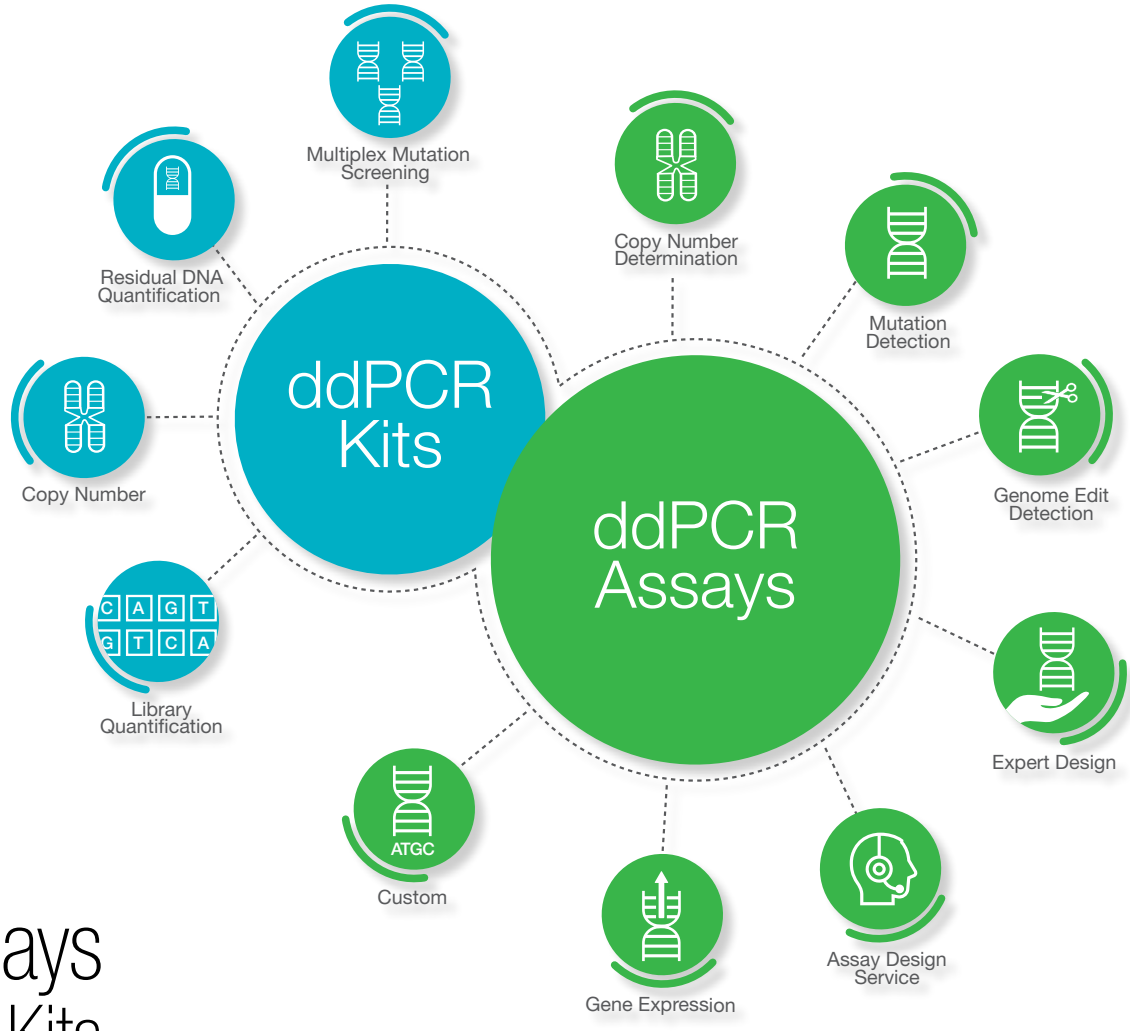
QXDx Universal Kit for AutoDG ddPCR System

QXDx Software

This is an IVD software with 2 modules: QXDx Acquisition for data acquisition and instrument controls and QXDx Analysis for data analysis and result reporting for QXDx BCR-ABL %IS Kit.

QXDx Developer Software

This research use only software provides users with greater flexibility to develop their own lab developed tests.



Assays and Kits

Clinical Research Assays

Bio-Rad has a broad portfolio of clinical research use assays, kits and services to facilitate lab developed testing.

These assays span Mutation Detection, Copy Number Determination, Gene Expression and Genome Edit Detection.

These kits span multiplex mutation screening, copy number, residual DNA quantification and library quantification.

Services include expert design, assay design service and custom design service.

Clincial Research Use Kits

Available research use only kits include multiplex mutation screening, copy number, and residual DNA quantification kits.

Assay Creation Services

Dozens of expert design assays (for research only) have been designed by Bio-Rad's Digital PCR experts for collaborations or key applications. Bio-Rad's ddPCR specialists offer design assistance through the Assay Design Service, or you can design an assay online yourself through the Digital Assay Site.

*See **www.bio-rad.com/digital-pcr-assays** for a full list of digital PCR assays.*

Ordering Information

Catalog No.	Description
Automated Testing System	
17005351	QXDx AutoDG ddPCR System ..... 1 unit *(Includes the QXDx Automated Droplet Generator, QXDx Droplet Reader, QXDx Acquisition/Analysis Software and QXDx Laptop)*
1814000	PX1 PCR Plate Sealer ..... 1 unit
NA	Thermal cycler with the following specifications: ■ Accuracy: +/– 0.2°C ■ Uniformity: +/– 0.4°C well-to-well within 10 sec ■ Adjustable ramp rate: up to 2°C/sec ■ Temperature range: 0-100°C ■ Ability to cool plate to 4ºC post run
Universal Reagents and Consumables	
17001378*	QXDx Universal Kit for AutoDG ddPCR System (Coming Soon) ..... 1 unit
12001922	QXDx AutoDG Consumable Pack ..... 480 reactions
12003031	QXDx AutoDG Supermix Pack (Coming Soon) ..... 480 reactions
12002526	QXDx Droplet Reader Oil Pack ..... 864 reactions
IVD Kits	
12005660	QXDx BCR-ABL %IS Kit IVD ..... 192 reactions
12010706	QX Developer Software (Coming Soon) ..... 1 unit
Recommended Materials	
1851197	C1000 Touch Thermal Cycler with 96-Deep Well Module ..... 1 unit

* Includes QXDx Consumable Pack, Supermix Pack, and Droplet Reader Oil Pack.

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