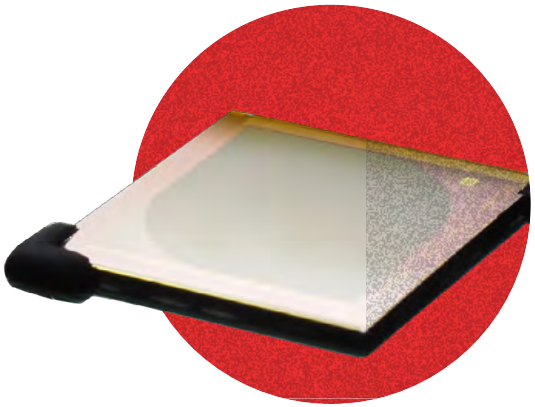
invitrogen

YOUR SONG. OUR SOUNDBOARD.

You provide the sequence. We produce the genes. GeneArt Gene Synthesis—not a note out of place.

ThermoFisher SCIENTIFIC



Contents

Why choose GeneArt Gene Synthesis?

Introduction

Lacking the time to clone your gene? Conventional PCR and cloning techniques require optimization and troubleshooting, which take up valuable lab time and resources. What if you could have your favorite gene made for you—analogous to an optimized, error-free PCR reaction? This is where gene synthesis comes in. It's simply molecular cloning made easy.

Whether you need industry-leading gene synthesis services or optimized protein expression, or want to outsource the entire process from gene synthesis to protein production, Invitrogen™ GeneArt™ products and services can help you succeed.

Here's a step-by-step guide to a typical Invitrogen™ GeneArt™ Gene Synthesis workflow:

Design

Use rational design software such as the Invitrogen™ GeneArt™ GeneOptimizer™ software to optimize gene expression.

Construct

Whether you outsource to us or do it yourself, select from our leading line of GeneArt products and services for optimal speed, quality, and performance.

Express

From small-scale research to industrial production in applied markets, put it all together with a complete toolbox of products and services for cell line development and growth, as well as protein expression and production.

GeneArt product portfolio

We are your partner for gene synthesis through protein production

GeneArt Gene Synthesis

A reliable and cost-effective method for obtaining customized DNA constructs with 100% sequence accuracy, GeneArt Gene Synthesis offers:

- Leading reliability in both delivery and performance
- Gene optimization for maximum protein expression
- The largest capacity and fastest production processes
- High quality—ISO 9001:2015 certification

GeneArt custom services

Whether you're looking to save time or improve upon existing processes, GeneArt services provide:

- A single resource for all of your outsourcing needs
- Expertise in gene synthesis, custom cell lines, and mammalian–baculovirus protein production
- Cloning and plasmid prep services
- ISO 9001:2015 certification with agile and responsive project management

GeneArt Strings and High-Q Strings DNA Fragments

An economical and time-saving alternative to PCR that maintains the GeneArt Gene Synthesis benefits of flexibility, superior performance, and exceptional accuracy. Invitrogen™ GeneArt™ Strings™ and GeneArt™ High-Q Strings™ DNA Fragments are compatible with any downstream cloning method.

- GeneArt Strings DNA Fragments are available up to 3 kb with a fast production time
- GeneArt High-Q Strings DNA Fragments offer unparalleled accuracy with an average error rate of <1 in 10,000 bp for constructs up to 1.2 kb
- Simply enter, edit, optimize, and order your sequence using the Invitrogen™ GeneArt™ Strings™ Assistant on Connect, our cloud-based platform

GeneArt Directed Evolution

Directed evolution is a powerful method used to create biomolecules for basic research, medical science, and industrial production. Invitrogen™ GeneArt™ Directed Evolution for protein engineering overcomes many of the limitations of conventional construction techniques for gene variant libraries. *De novo* gene synthesis enables construction of virtually any gene variation so that your library encodes maximum variability. GeneArt Directed Evolution services include:

- Invitrogen™ GeneArt™ combinatorial libraries
- Invitrogen™ GeneArt™ site-directed mutagenesis

GeneArt Gene Synthesis site

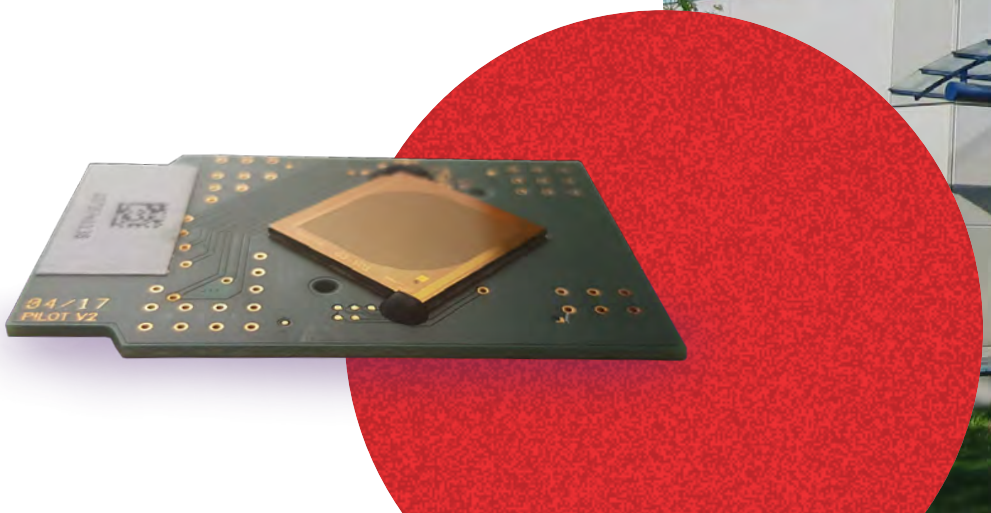
Our Global Centers of Excellence for gene synthesis services are located in Regensburg, Germany

GeneArt products and services have provided superior gene synthesis solutions for researchers around the globe. Our Regensburg site provides the market with ~11 million bp on a monthly basis and is certified by the International Organization for Standardization (ISO). We're constantly expanding the capacities of this site to meet the growing market demand for synthetic genes. More than 300 employees worldwide are currently working to provide you with the best possible products and services.

A new way to synthesize genes

The Regensburg site is also the birthplace of our G3 platform*—the highly innovative and cutting-edge, proprietary technology using a combination of miniaturization, automation, and NGS to provide unparalleled accuracy, reliability, and performance in the industry (Figure 1).

* Kuhn P et al. (2016) Next generation gene synthesis: From microarrays to genomes. *Eng Life Sci.* doi.org/10.1002/elsc.201600121.



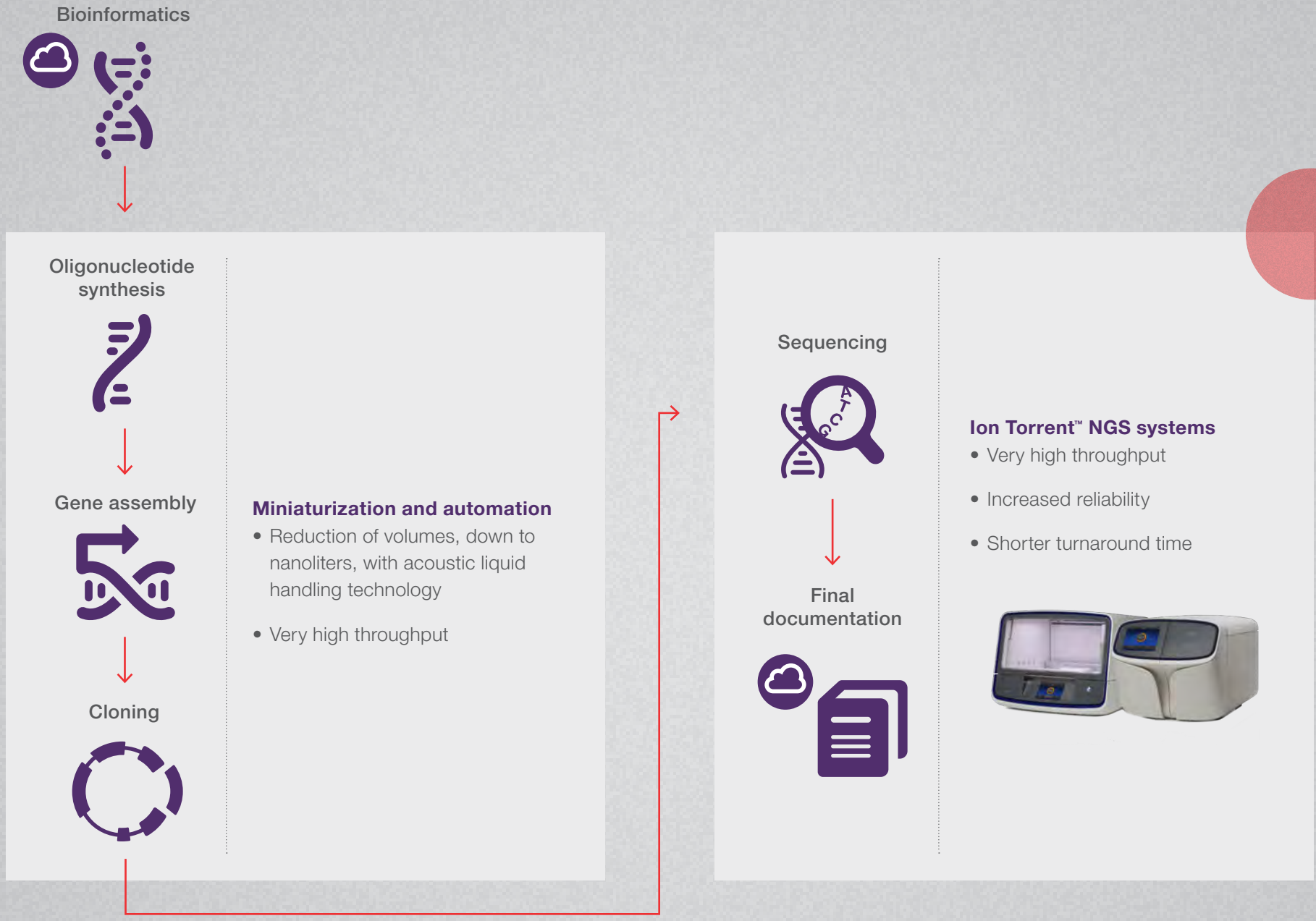


Figure 1. The G3 synthesis workflow.

GeneArt Gene Synthesis

High-quality custom gene synthesis

GeneArt Gene Synthesis services offer ease, flexibility, and reliability for your daily DNA work. Gene synthesis is a cost-effective, time- and resource-saving method for obtaining your desired DNA construct with 100% accuracy (Figure 2). It is a true alternative to conventional molecular biology techniques, while enabling better, more reliable protein expression and quality. GeneArt Gene Synthesis tools go beyond traditional gene synthesis by enabling expression optimization for maximum performance.

Features

- Proprietary optimization of expression and mRNA stability
- Nearly unlimited flexibility in gene and vector design
- Empirically proven increase in protein expression
- Ready-to-use constructs for expression and transfection
- Easy online ordering
- Project setup assistance and individual project support
- Maximum performance using the proven GeneArt GeneOptimizer algorithm
- Maximum production speed and worldwide delivery; capacity and reliability supported by a fully automated, industrial-scale gene processing platform

* Production time is the number of business days required to synthesize GeneArt genes in our manufacturing facility. Delivery time is in addition to production time and depends on the destination of the shipment. Turnaround time is production time plus delivery time.
** There is an upgrade fee for Express and SuperSPEED deliveries.

Timely production

Visit **thermofisher.com/genesynthesis** for the latest updates on turnaround time.

Standard*
- Up to 1,200 bp in 9 business days
- Up to 3,000 bp in 12 business days

Express**
- Up to 1,200 bp in 7 business days
- Up to 3,000 bp in 10 business days

SuperSPEED**
- Up to 1,200 bp in 5 business days
- Up to 1,800 bp in 7 business days

Quality

- All processes are ISO 9001:2015 certified
- Comprehensive quality documentation included
- Automated production processes
- 100% sequence validation

For more information, email **geneartsupport@thermofisher.com**

Complete solutions from fragments to genome assembly, single clones to plates

- High-throughput gene synthesis with a capacity of >11 Mbp per month
- Expert design and assembly technologies, and process expertise for the assembly of constructs from ten to several hundred kilobases
- Robust technologies for building DNA constructs with the highest complexity
- Flexible sequencing solutions for sequence verification and final QC
- Proven track record of reliable and timely production for long and complex constructs
- Assembly kits that enable do-it-yourself construction and assembly

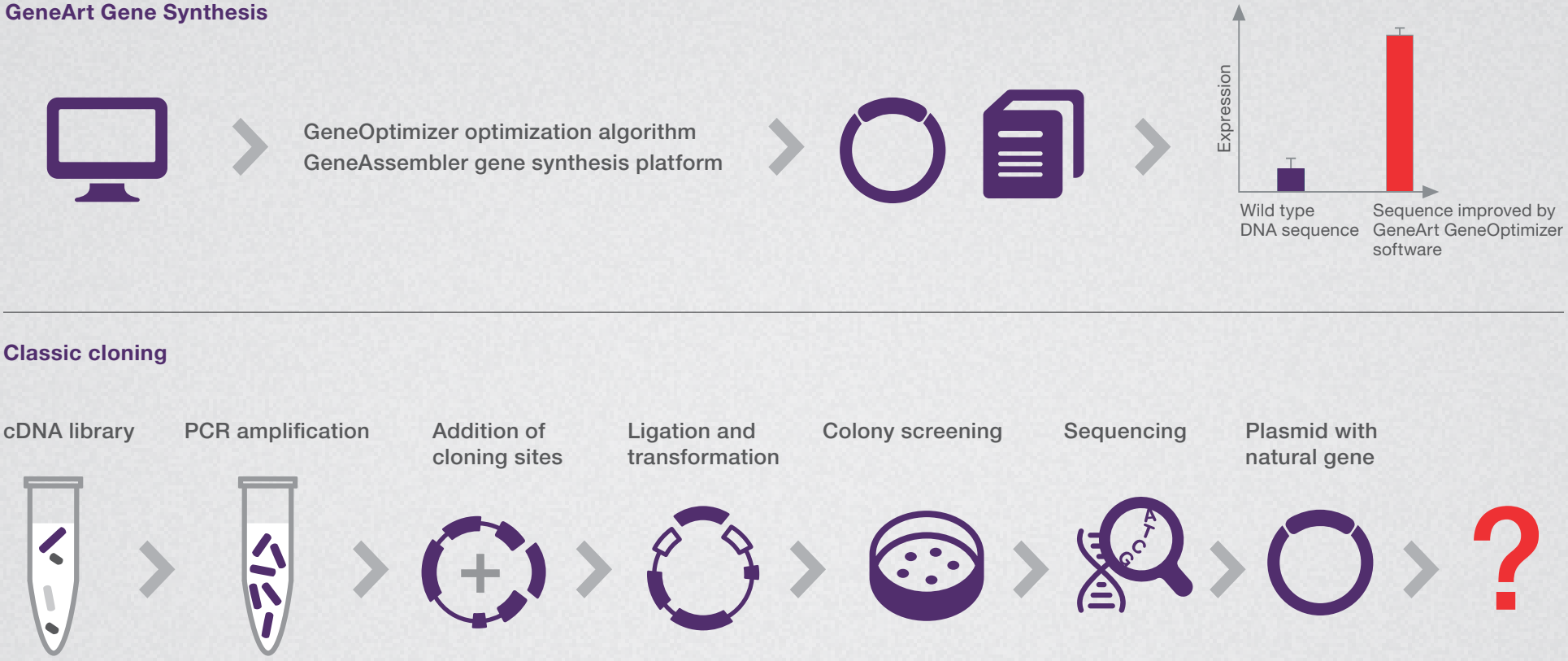


Figure 2. GeneArt Gene Synthesis and optimization are faster than classic cloning methods and can provide better results.

Find out more at **thermofisher.com/genesynthesis**

GeneArt Strings DNA Fragments

GeneArt Strings DNA Fragments are custom-made, uncloned, double-stranded linear DNA fragments up to 3,000 bp in length, assembled from synthetic oligonucleotides using the same high-quality process developed for GeneArt Gene Synthesis (Figure 3). Strings DNA Fragments are delivered dried and ready for resuspension, cloning, and screening for identification of the correct clone. They are a fast and smart alternative for getting your synthetic gene cloned into your expression plasmid (Figure 4).

Affordable

GeneArt Strings DNA Fragments are a cost-effective alternative to gene synthesis

Flexible

Full gene design and cloning flexibility; clone with any downstream method of choice

Fast

At least 200 ng of GeneArt Strings DNA Fragments are produced within 3–5 business days* (for up to 1,000 bp) or 6–8 business days (for 1,000–3,000 bp)*

Optimized

GeneArt GeneOptimizer software helps ensure maximum protein expression

Streamlined

Enter your sequence and directly edit, optimize, and order through our online GeneArt portal

* Depending on the nature of the sequence, production time can vary. Delivery times are in addition to the specified production times and depend on location.

Find out more at **thermofisher.com/strings**

GeneArt Strings DNA Libraries

Invitrogen™ GeneArt™ Strings™ DNA Libraries are GeneArt Strings DNA Fragments with randomized nucleotides, providing a cost-effective alternative to complete combinatorial libraries, with a shorter turnaround time. They consist of pools of custom-made fragments of 200–2,000 bp and can be used for antibody and protein engineering or other applications.

- Add up to three blocks of degenerate nucleotides with randomized distribution
- Each block can consist of up to 30 bp using full IUPAC code of DNA nucleotides
- Ready for cloning and screening
- At least 500 ng produced within 10–15 business days

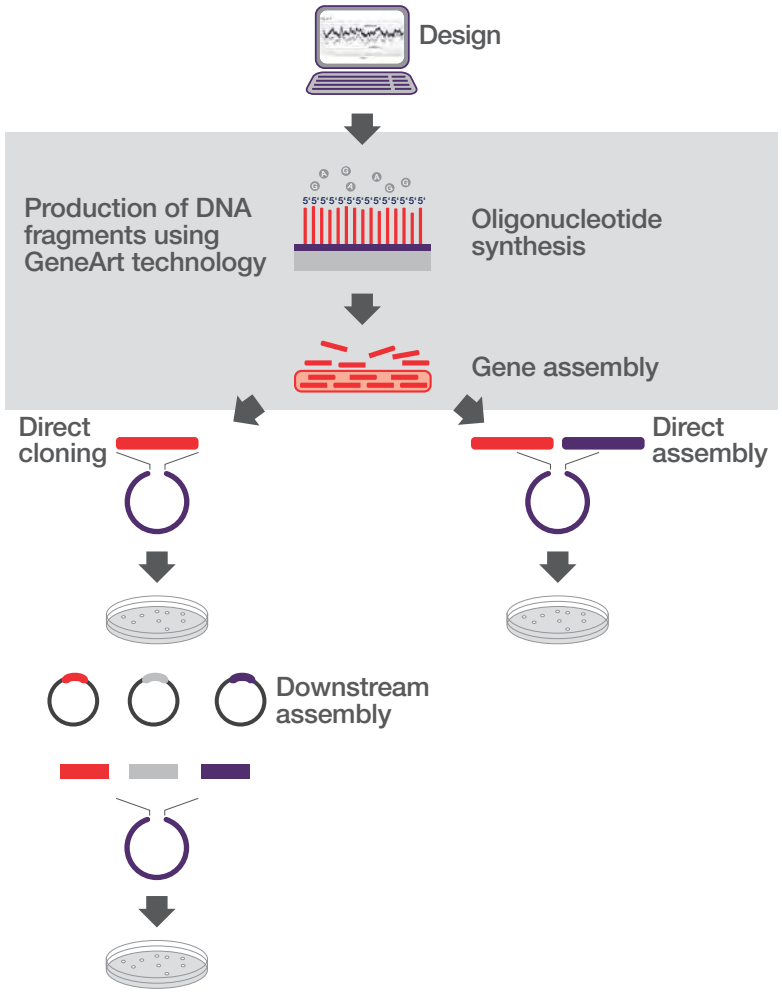


Figure 3. Producing a synthetic gene using GeneArt Strings DNA Fragments.

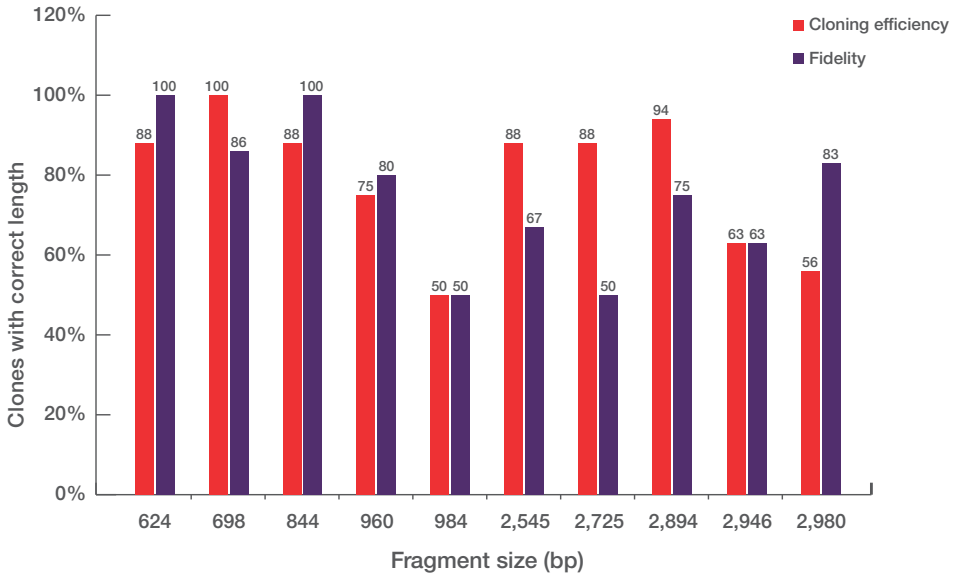


Figure 4. Ten GeneArt Strings DNA Fragments up to 3,000 bp were cloned using the Invitrogen™ GeneArt™ Seamless Cloning and Assembly Kit. Figure shows the percentages of clones with correct length as identified by colony PCR (cloning efficiency), and the percentages of clones with correct sequence (fidelity) based on the number of full-length clones.

See the data

See how GeneArt Strings DNA Fragments compare to other suppliers' products.

Download our white paper at **thermofisher.com/strings**

GeneArt High-Q Strings DNA Fragments

GeneArt High-Q Strings DNA Fragments are revolutionary custom DNA fragments developed to provide unparalleled sequence accuracy and quality in the industry. Our cutting-edge and innovative microchip technology platform coupled with high accuracy standards result in an error rate of less than 1 in 10,000 bp. This unrivaled accuracy makes them ideal for multifragment, high-order assembly using Invitrogen™ GeneArt™ assembly kits.

GeneArt High-Q Strings DNA Fragments reduce the required screening effort by at least 60% compared to other suppliers and enable direct assembly of 5 kb constructs with reasonable screening effort (Figure 5).

- Leading accuracy in the market, with an error rate of less than 1 in 10,000 bp
- Flexibility to place orders ranging from single constructs to high-throughput quantities
- Direct use for high-throughput assembly, no universal linker that needs intermediate cloning
- Production time similar to cloned gene synthesis constructs

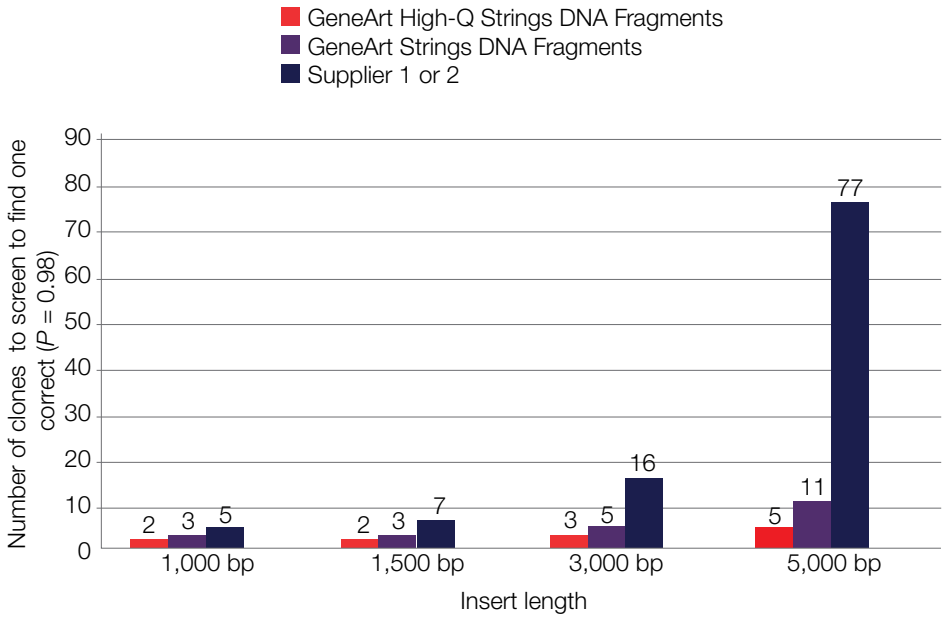


Figure 5. Reduce the number of clones that need to be sequenced in order to identify a correct clone with a probability of 98%. With a 1,000 bp insert length, we needed only two clones with the GeneArt High-Q Strings DNA Fragments vs. five clones with another supplier's product—resulting in a 60% reduction in screening effort.

Choosing which DNA fragment type is right for you

	GeneArt High-Q Strings DNA Fragments	GeneArt Strings DNA Fragments
How to order	GeneArt Strings Assistant	GeneArt portal or GeneArt Strings Assistant
Benefits	Unparalleled accuracy	Faster turnaround time
Length	200–1,200 bp	200–3,000 bp
Accuracy (error per base)	Less than 1 in 10,000	Less than 1 in 5,000
GC content	30–70% GC (some homopolymers excluded)	30–70% GC
Total reliability	95%	95%
Production time	6 to 9 business days	3 to 8 business days
Delivery amount (lyophilized DNA)	Minimum >200 ng	Minimum >200 ng
	Average 900 ng	Average 900 ng

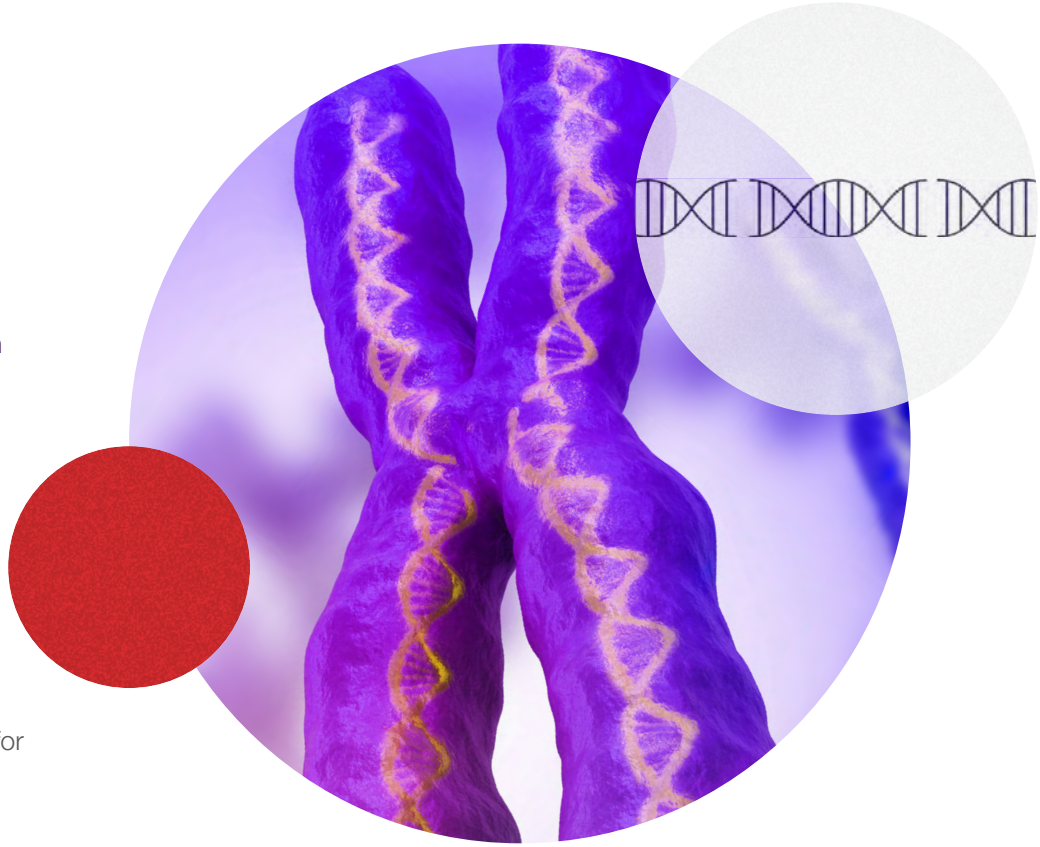
See the data

See how GeneArt High-Q Strings DNA Fragments compare to other suppliers' products.

Download our white paper at **thermofisher.com/highqstrings**

Gene optimization

Maximize protein expression



Experience enhanced protein expression based on gene optimization
Gene optimization is the solution to the limitations of traditional protein expression. Common pain points associated with protein expression, such as yield, can now be addressed in a rational and systematic way. Using data available from published literature in combination with proprietary data, the GeneOptimizer algorithm determines the optimal gene sequence for your expression experiments (Figure 6).

GeneArt GeneOptimizer sequence processing:

- Identifies the best way to incorporate your requested sequence elements
- Eliminates cryptic splice sites and mRNA-destabilizing sequence elements for increased mRNA stability
- Optimizes codon usage and adapts GC content to your expression system
- Avoids undesirable mRNA secondary structures
- Eliminates repetitive sequences
- Includes siRNA-resistant forms of wild type genes that can be used in RNAi rescue experiments

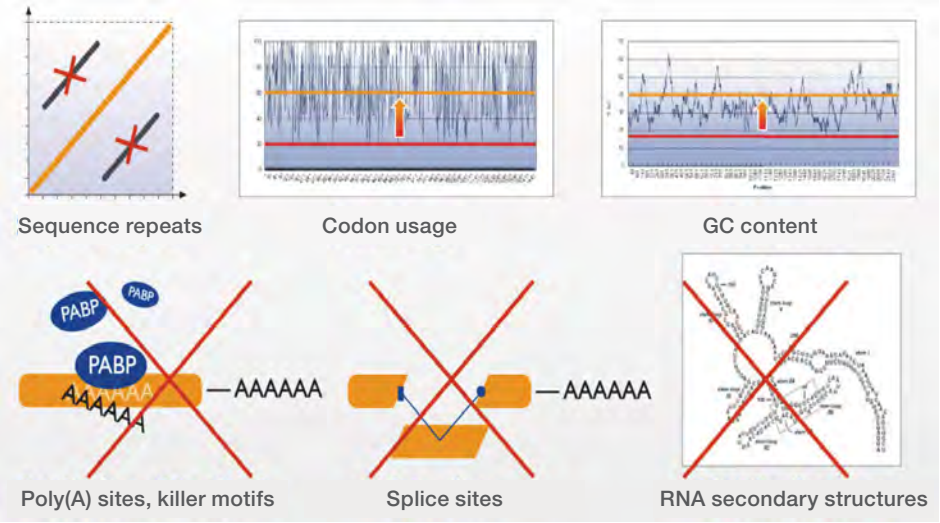


Figure 6. The GeneOptimizer algorithm determines the optimal gene sequence for your experiments. The algorithm takes many factors into account—for example, it removes DNA sequence repeats, optimizes codon usage and GC content, and minimizes the formation of RNA secondary structures that may reduce protein yield. Protein sequence is not affected by the optimization process.

Up to a 100-fold increase in expression

The GeneOptimizer process has been shown to help deliver large increases in protein yield via a combination of factors that stabilize mRNA and maximize translation efficacy (Figure 7). Optimization has been experimentally proven to increase protein expression up to 100-fold in a variety of host systems.*

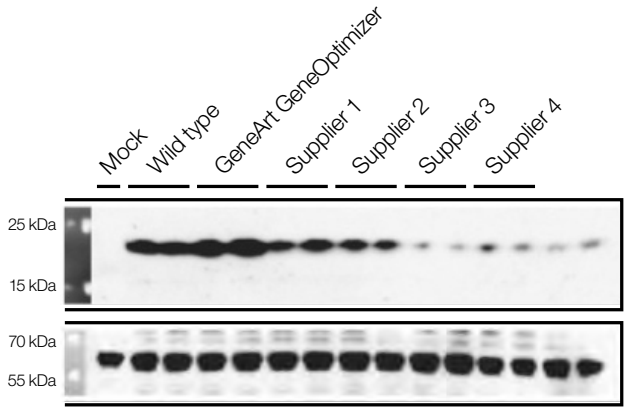


Figure 7. Comparative expression analysis of wild type vs. an optimized human gene. Based on western blot analysis using an α-His antibody, expression levels of two independent transfections per wild type and optimized construct are displayed, showing a three-fold difference in expression in this particular analysis. Standardization is based on endogenous protein.

* Fath S, Bauer AP, Liss M, et al. (2011) Multiparameter RNA and codon optimization: A standardized tool to assess and enhance autologous mammalian gene expression. *PLoS One* 6(3):e17596.

Find out more at **thermofisher.com/geneoptimization**

Expression-ready genes

GeneArt Express cloning service

With our Invitrogen™ GeneArt™ Express cloning service, you can save 4–5 days of turnaround time and receive expression-ready genes faster by choosing express cloning into selected Invitrogen™ vectors (Figure 8). Simply order via the online GeneArt portal and add the Express cloning service to your gene synthesis request. You will receive your synthesized gene in the selected expression vector, without the intermediate pMX vector that is delivered with subcloning services.

Turnaround time for gene synthesis and Express cloning starts at 11 business days. Adding gene synthesis Express delivery* in addition to Express cloning saves an additional 2 days, so it is possible to realize a turnaround time of 9 business days for your cloned, expression-ready gene. In order to qualify for Express cloning, genes must be <5 kb and must not contain complex sequences. (Optimization of your sequence with GeneOptimizer software in the GeneArt portal can reduce complexity.)

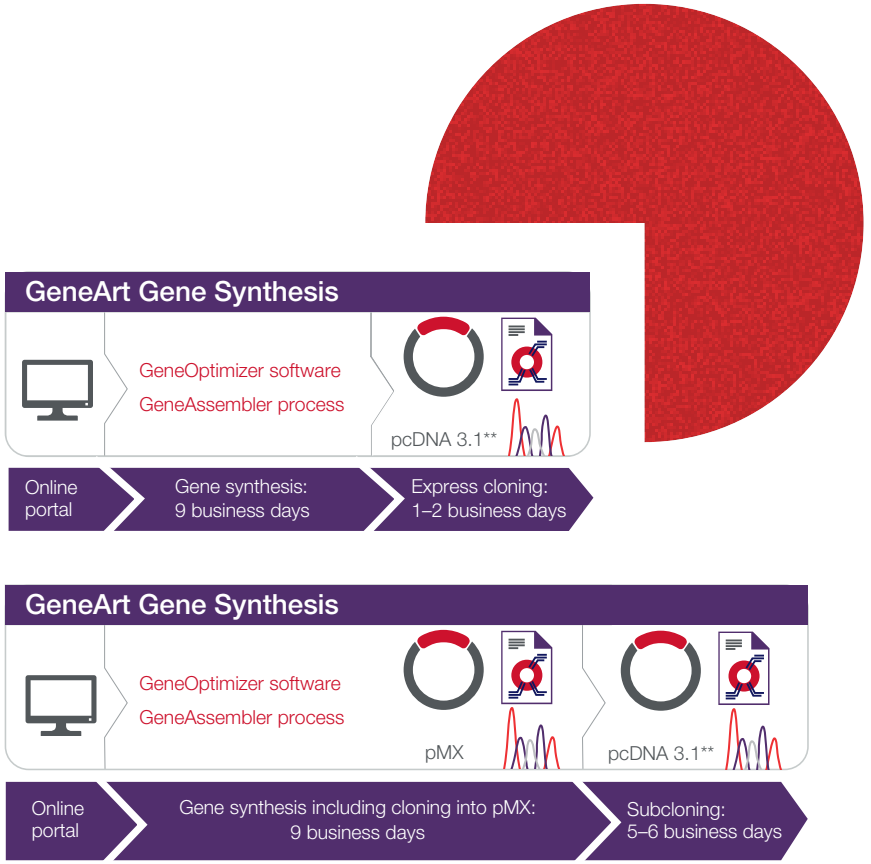


Figure 8. Express cloning directly into an expression vector (top) compared with classic subcloning from pMX into an expression vector (bottom).

** Expression vector example. Multiple choices for vectors are available.

* There is an upgrade fee for Express delivery.

Find out more at **thermofisher.com/expressgenes**

Cloning and plasmid services

GeneArt Subcloning Service

Get your gene ready to use in your downstream applications. After gene synthesis, our Invitrogen™ GeneArt™ Subcloning Service can subclone your gene into any vector you send us, and we will store the plasmid for future subcloning projects. We also have our own vectors in stock for you to choose from. Even complex cloning projects with multiple open reading frames are no problem (e.g., large double-gene vectors expressing monoclonal antibodies).

If desired, we also deliver a customized production report detailing the reagents we used and the lot numbers. Focus on your results and leave the subcloning to GeneArt services.

Benefits

- Convenient—tell us what you need and receive your ready-to-use clone quickly
- Reliable—inserts are 100% sequence-verified and documented
- Sole provider of Invitrogen™ Gateway™ recombination cloning technology
- Confidential—no data or material are provided to third parties
- Extendable—order a plasmid prep

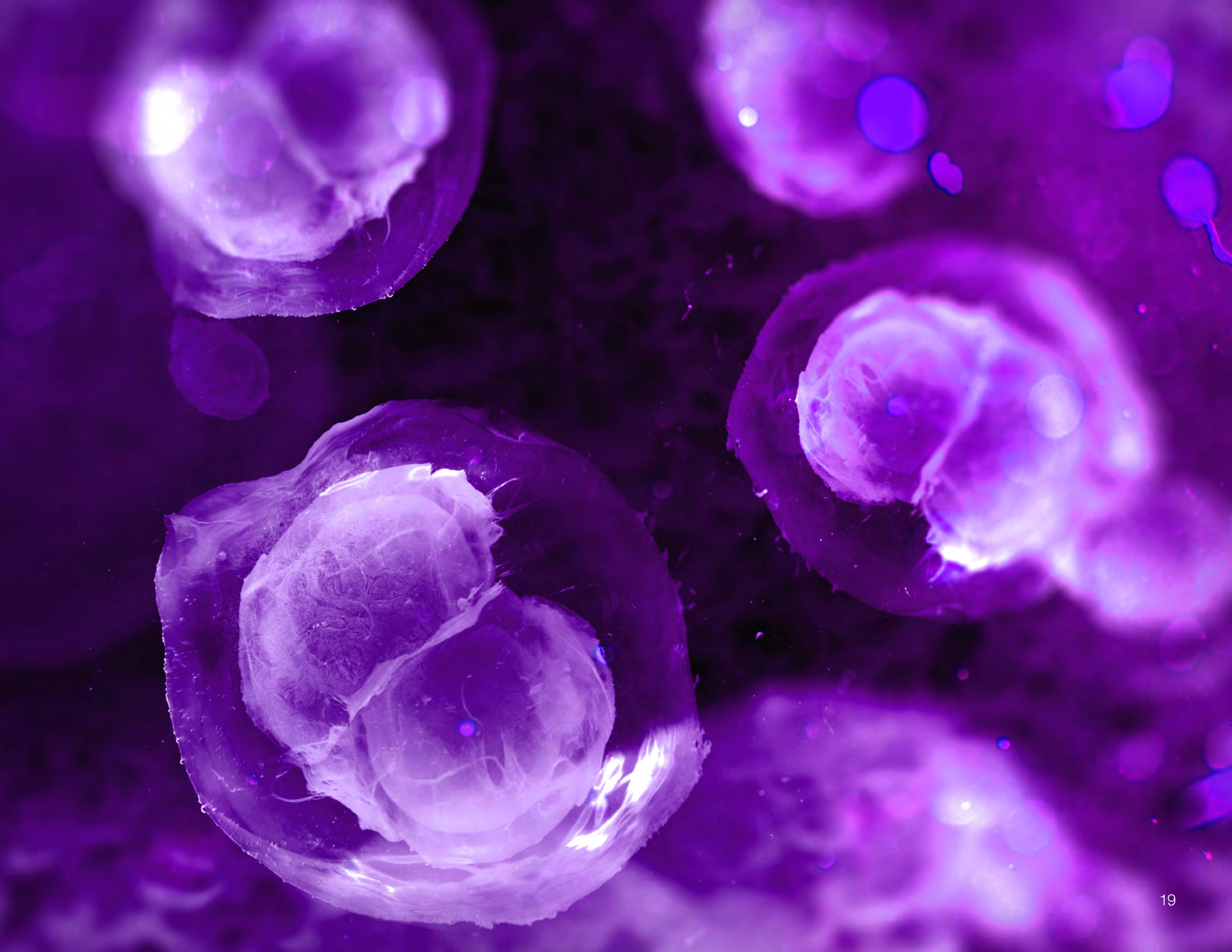
GeneArt Plasmid Service

DNA prepared by the Invitrogen™ GeneArt™ Plasmid Service is consistently of high quality and can be used for research applications and preclinical studies. From vector construction to the production of plasmid DNA, GeneArt plasmid services make the development and execution of your project easy.

High-quality, scalable plasmid DNA preparation

- Highly pure and homogeneous plasmid DNA
- Low levels of endotoxin (down to 0.01 EU/µg DNA)
- Scale up to 20 mg
- Fill-and-finish service (receive your DNA aliquoted and labeled for immediate use, per your specifications)
- 2D matrix tube and plate delivery options

A Certificate of Analysis (CoA) is provided with every plasmid order.
Find out more at **thermofisher.com/geneartplasmid**



Gene-to-protein and gene-to-cell line services

Gene-to-protein service

Starting with only a nucleotide sequence, GeneArt services can typically provide purified protein within 30 business days. Production and purification from mammalian suspension cells (Gibco™ FreeStyle™ 293, FreeStyle™ CHO, Expi293™, and ExpiCHO™ cells) or baculovirus expression systems (Sf9 and Sf21) help ensure correct protein folding and processing. The combination of optimized genes with our advanced expression systems usually leads to higher protein yields than are achievable with other expression systems and wild-type genes.

Service types

Culture volume–based service:

- Protein expression and affinity purification from customer-specified culture volume
- Deliverables are the purified protein and a comprehensive report, including Coomassie™ blue–stained gel and western blot with affinity tag–detected protein

Verified protein amount service:

- Protein expression and affinity purification of customer-specified protein amount are verified
- Pilot project with culture volume–based service is required to evaluate the expression yield per liter
- Deliverables are the purified protein and a comprehensive report, including Coomassie blue–stained gel and western blot with affinity tag–detected protein
- Additional purification steps and analytics are possible

Benefits

- **Seamless project processing**—gene synthesis and protein purification from one source
- **Speed**—from gene to protein within 30 business days (typical)
- **Increased protein yield**—combination of optimized genes and advanced expression systems routinely leads to increased expression
- **Improved protein expression**—optimized genes can show expression of otherwise non-expressible proteins
- **Full process transparency and transferability**—use of our commercially available reagents and protocols; delivery of optimized gene in expression vector together with the purified protein
- **Comprehensive documentation**—every protein comes with a detailed report; analytical SEC or other advanced analytics optionally available
- **Experienced team**—routine handling of multiple large projects with tight timelines

Gene-to-cell line service

We use the Gibco™ Freedom™ CHO DG44 system to generate cell lines with high levels of protein expression (e.g., antibodies in milligram to gram-per-liter range).

- Generation of Invitrogen™ Flp-In™ expression cell lines based on existing host cell lines using expression-optimized genes
- Generation of monoclonal CHO cell lines for high-level protein expression

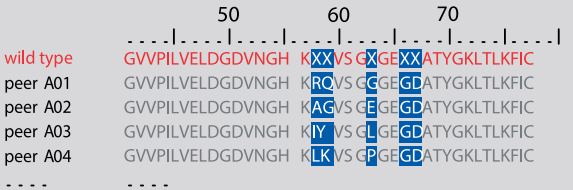
For more information, email **geneartprotein@thermofisher.com** or go to **thermofisher.com/g2pservice**

Creating improved proteins

GeneArt Directed Evolution

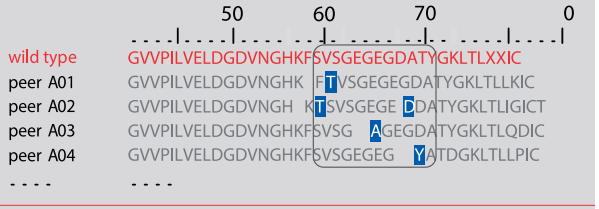
Combinatorial libraries

True rational design for defined randomization of selected sites only, while providing maximum framework integrity.
Benefits: low ancillary mutation rates and high diversity, quality control by next-generation sequencing (NGS) available
Applications: construction of recombinant antibody libraries, promoter libraries, and combining of substitutions identified by site-directed mutagenesis



Controlled randomization libraries

Substitute any amino acid in a gene with a defined probability.
Benefits: accurate fine-tuning of mutation rate, and randomization of the entire open reading frame
Applications: affinity maturation of antibodies, improvement of industrial enzymes, and modification of enantioselectivity of enzymes

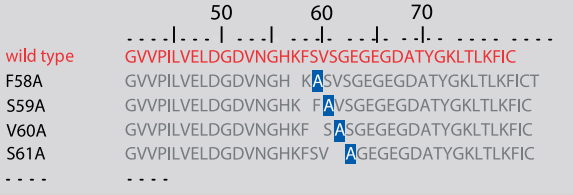


Site-saturation mutagenesis

Scanning a protein region by site-saturation mutagenesis identifies all beneficial substitutions for enhanced function.
Benefits: best cost efficiency, with no structural data needed for protein improvement
Applications: improvement of industrial proteins and alienation of proteins from patented sequences

Site-directed mutagenesis

Introduce single or multiple mutations (substitutions, insertions, or deletions) into existing DNA sequences.
Benefits: fully sequence-verified clones, no unwanted backbone mutants, and fast turnaround times
Applications: construction of fusion proteins, tagged proteins, alternative splice forms, and alanine scans



Find out more at **thermofisher.com/directedevolution**

The online GeneArt portal and Instant Designer

The GeneArt Gene Synthesis online sequence design and ordering portal (GeneArt portal) offers convenient and simple ordering of your gene synthesis projects. This automated portal helps you enter, edit, and optimize your sequences, and offers immediate price quotes and ordering capabilities. Nearly all of the GeneArt services can be ordered using this intuitive ordering tool. You can even perform *in silico* cloning and store your gene sequences, projects, and personal vectors for future design. Save time and have full control and flexibility with this one-stop shopping feature.

Project Manager allows for simple and easy project creation—build out your individual product requirements with the icon-based Project Configurator (Figure 9).

See our library of videos on using the GeneArt portal, including overview, setup, quick order, optimization, and subcloning services, at **thermofisher.com/genearttutorials**.

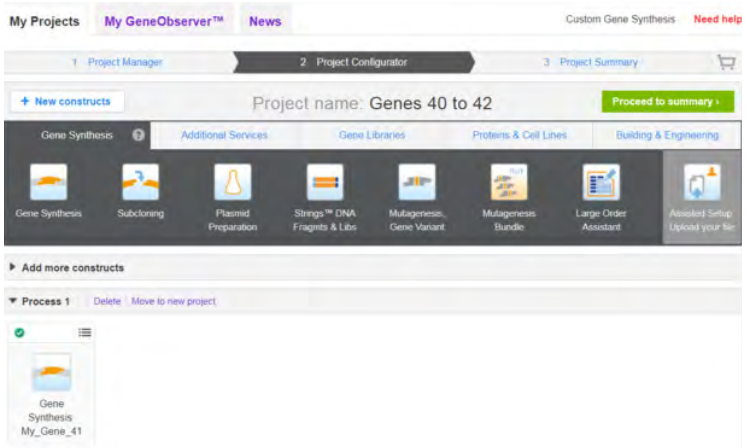


Figure 9. Project Configurator in the GeneArt portal.

New: Introducing the GeneArt Instant Designer

The Invitrogen™ GeneArt™ Instant Designer offers a streamlined and redefined ordering experience for GeneArt Gene Synthesis products. The GeneArt Instant Designer offers a fresh, modern, intuitive interface that is built on Connect (Figure 10). Project Manager and Sequence Manager are now featured in the same view, with easy visibility into the estimated production time.

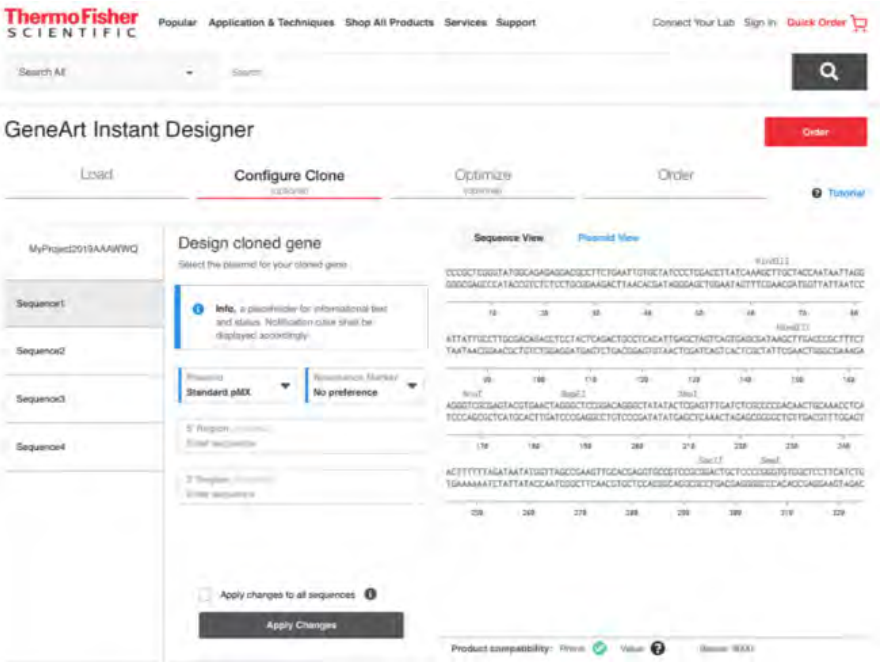


Figure 10. Intuitive interface for the GeneArt Instant Designer.

Value and Prime GeneArt Gene Synthesis services

Featured within the GeneArt Instant Designer are Value and Prime gene synthesis services that provide you with options based upon your project needs (Figure 11).

Value service	Prime service
Exclusively for online orders	Online and offline order options are available
Ideal for non-complex sequences	Applicable to both complex and non-complex sequences
Order genes 200–5,000 bp	Order genes 100–12,000 bp
Quality control with NGS	Quality control with NGS or Sanger sequencing
Ideal if you don't need additional services like Express or SuperSPEED	Add-on services and upgrades are available

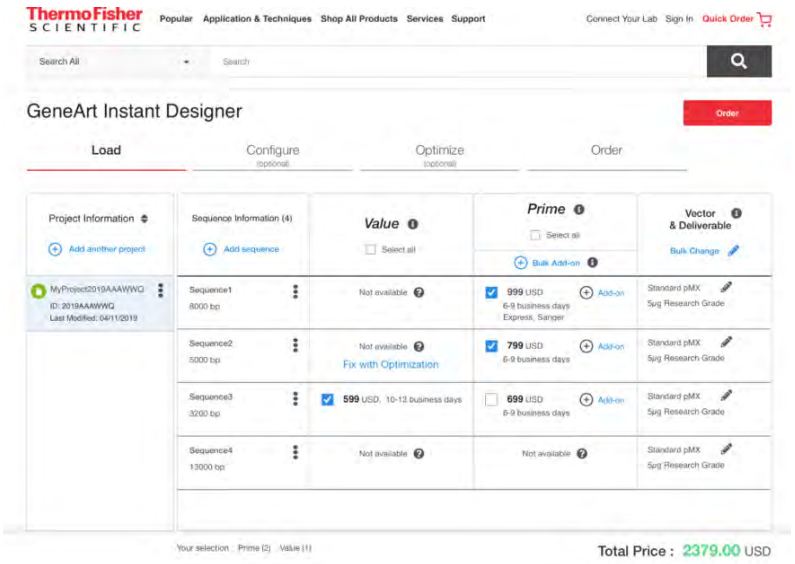


Figure 11. Value and Prime services available through the GeneArt Instant Designer.

Find out more at **thermofisher.com/genesynthesis**

GeneArt Strings Assistant

The GeneArt Strings Assistant on Connect identifies any potential regions of sequence complexity within your GeneArt Strings DNA Fragments or High-Q Strings DNA Fragments. If any regions of complexity are found within your DNA sequences, you can either manually edit them or follow the suggestions of the GeneArt Strings Assistant to rescue the sequence (Figure 12).

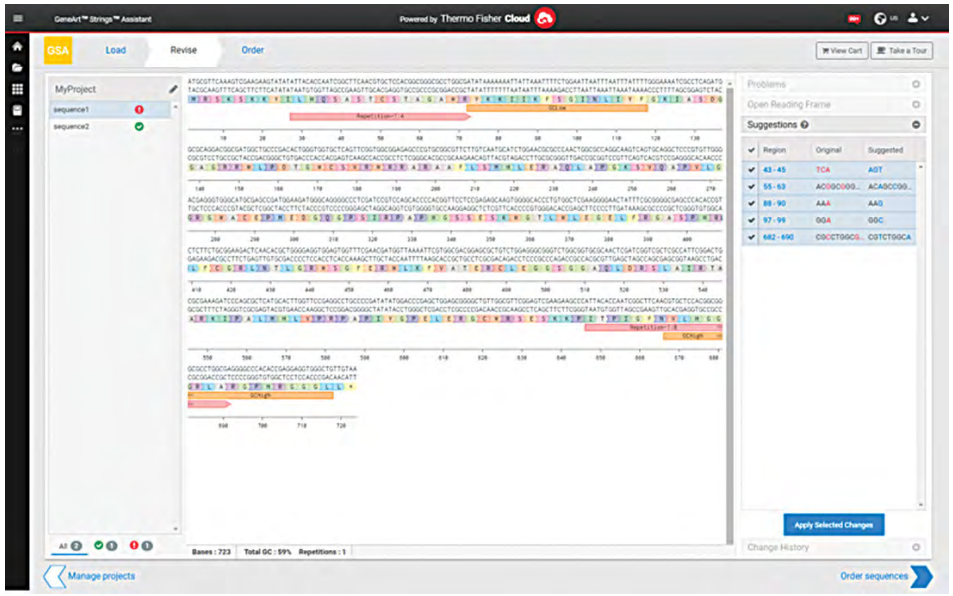
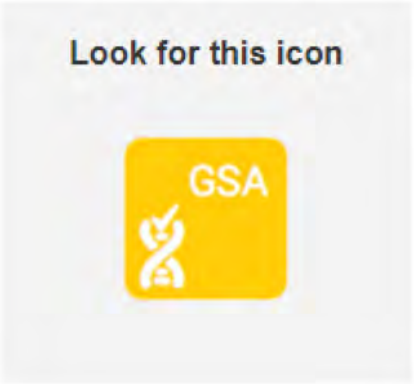


Figure 12. An example screenshot of the GeneArt Strings Assistant app. Regions of sequence complexity are highlighted, and suggestions are shown to the right.

Other key features:

- Order all prequalified sequences directly from within the GeneArt Strings Assistant, following the simple steps to checkout
- Determine if your sequence qualifies as a High-Q Strings fragment, with easy options to configure
- Review past and pending orders with the powerful project manager
- Select the organism you are targeting, to avoid rare codons as suggested by the GeneArt Strings Assistant



ISO certification

We adhere to specific quality management standards from ISO that help ensure stable, reproducible, and timely results for the reliable production of your gene sequence of interest. Our Regensburg manufacturing site is ISO 9001:2015–certified, as detailed in Figure 13.

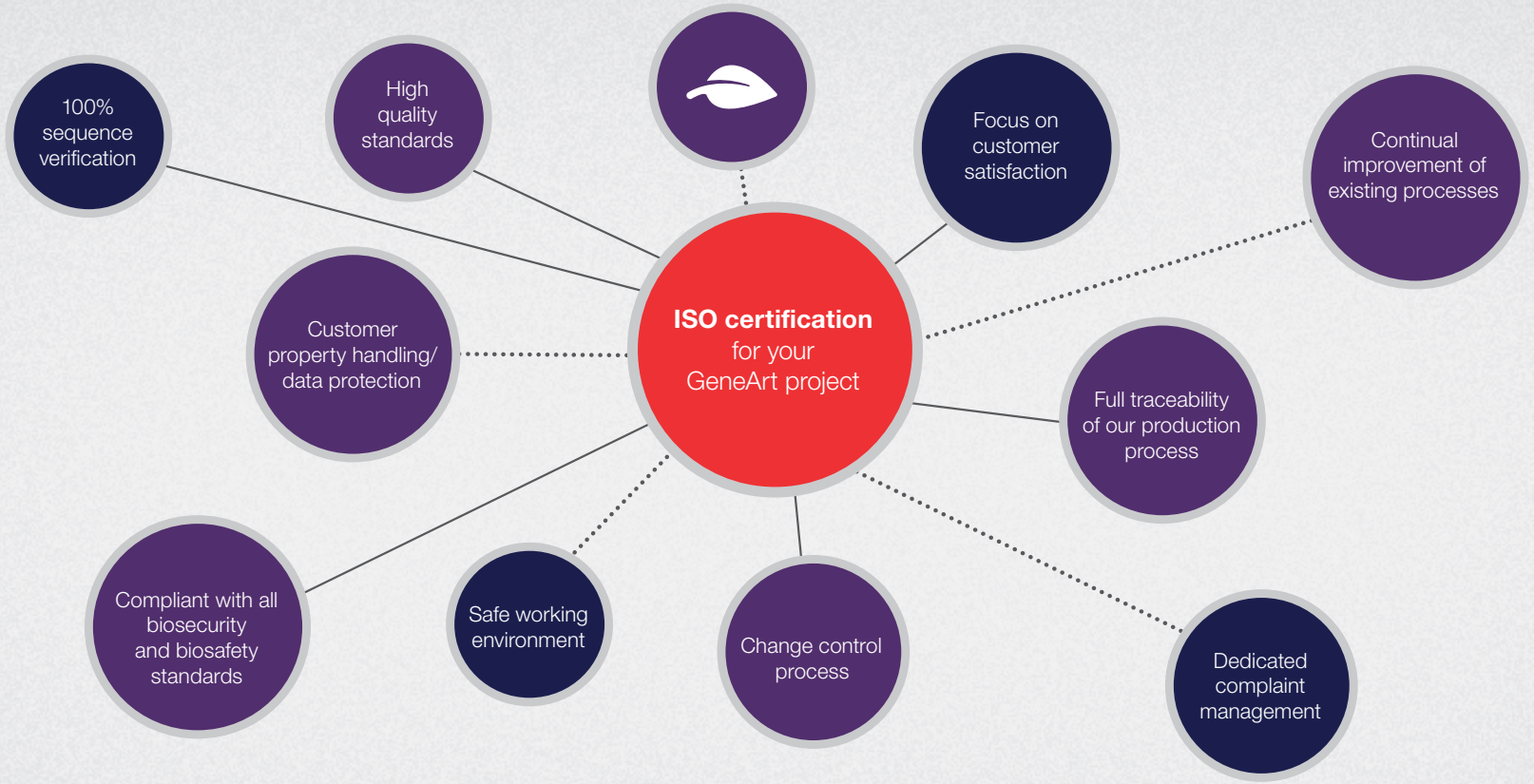


Figure 13. Overview of important criteria included in ISO certification, our everyday benchmark.

Our commitment to you and the environment

Sustainability matters to us

At Thermo Fisher Scientific, we take responsibility for our environmental impact. There is a growing amount of human-generated waste every year. Greater self-awareness by consumers is encouraging, but individuals are only part of a complex waste-reducing equation. Businesses must take stock, too.

As of 2019, we have 14 externally certified Zero Waste sites around the globe, including our production site for GeneArt projects in Regensburg.

How we are reducing waste

A site is designated Zero Waste after achieving 90% diversion of nonhazardous waste from landfill, and when waste is incinerated only as a last resort. For the facility in Regensburg, 0% of our waste goes to landfill. It is separated and recycled in a modern waste separation and power plant. These efforts are taken to avoid, reduce, reuse, and recycle as much as possible.

Here are some examples of how we've reduced waste:

Redesigned GeneArt product packaging

- Replaced the original 20-tube rack with an 8-tube rack, for a 54% reduction of weight and 1,100 kg reduction of cardboard
- Uses fully recyclable cardboard
- Increases functionality for customers

Developed an automated reagent transfer system for oligo synthesis

- Avoids manual handling of hazardous substances
- Reduces labor time
- Reduces glass waste by approximately 20 tons per year and cardboard waste by 4.5 tons per year
- Saves on costs of reagents and waste disposal

Enabled data transfer via Connect for Quality Assurance Documentation (QAD)

- Download QAD data from Connect instead of receiving a CD with the shipment; look for the GQ icon
- Eliminates CDs for QAD data, printed manuals, and product information

Customer support

We strive to provide the best customer experience whether you interact with us online or directly with our customer support team. Nearly all of our GeneArt services can be ordered using the GeneArt portal, Instant Designer, and GeneArt Strings Assistant, but we have a dedicated support team for your peace of mind.

GeneArt Gene Synthesis Customer Care Group

Our Gene Synthesis Customer Care Group is a single contact point, serving you from initial questions about products, technology, or online ordering, through the manufacturing process, up to final delivery of your gene construct. All of our customers across the globe have access to individualized project consulting—because we care about your projects.

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Find out more at **thermofisher.com/genesynthesis**

invitrogen

Related product information

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thermofisher.com/cloning

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