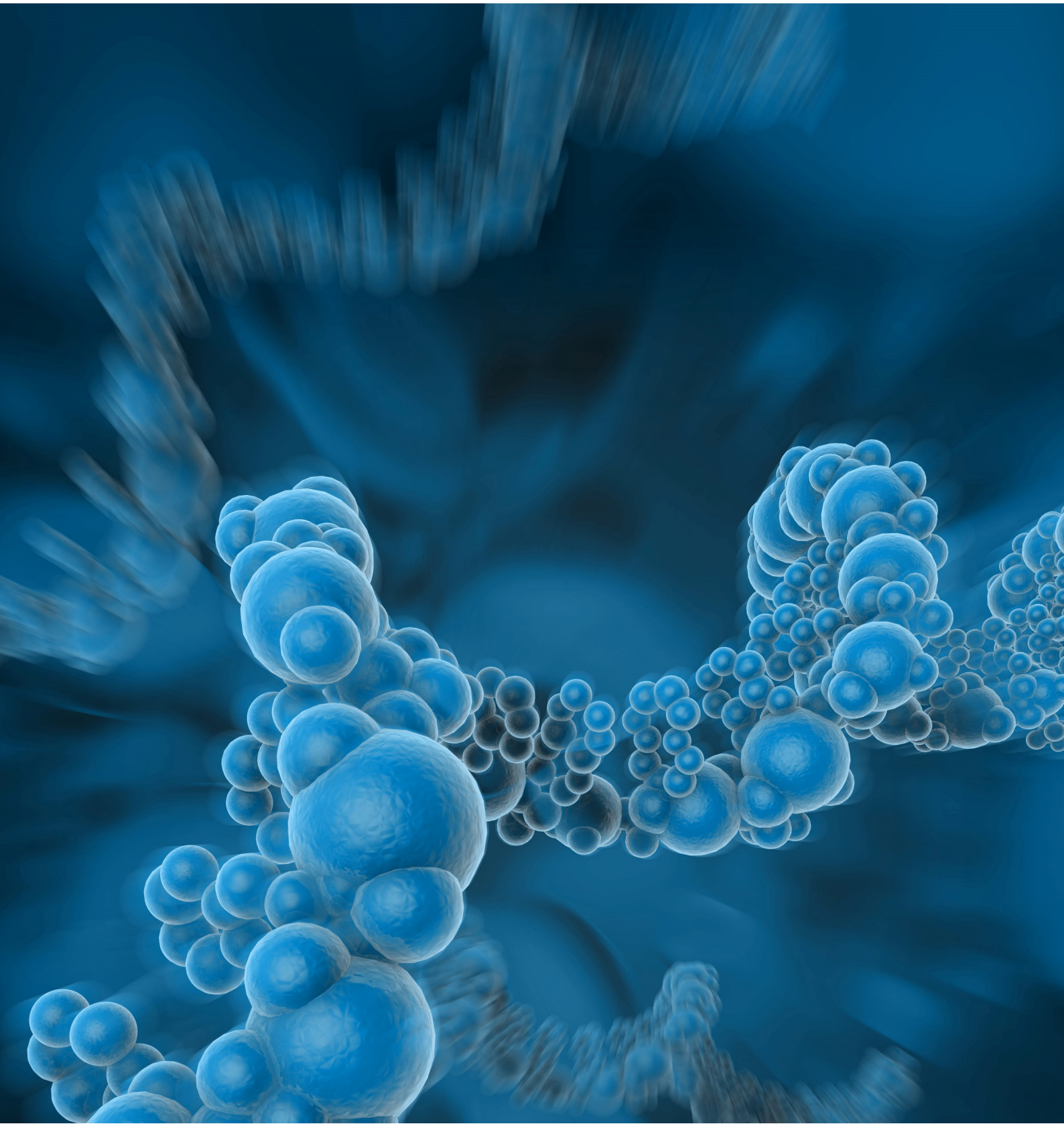
Microsynth

THE SWISS DNA COMPANY



CATALOG 2020/2021

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Microsynth – At a Glance

Microsynth AG is a privately held and independent Swiss biotech company in the area of nucleic acid synthesis & analysis employing more than 80 people. Microsynth AG has subsidiaries in Germany (Microsynth Seqlab GmbH), Austria (Microsynth Austria GmbH) and Switzerland (ecogenics GmbH).

Our History

Microsynth is a leading European company in the field of nucleic acid synthesis and analysis and is currently active in the following three business areas:

1. DNA/RNA synthesis
2. DNA/RNA analysis and sequencing
3. Contract research/outsourcing

Microsynth was founded in 1989 by Dr. Tobias Schmidheini as a spin-off of ETH Zurich. When Dr. Schmidheini started producing DNA oligonucleotides on behalf of Swiss academic institutes, he was one of the pioneers in this field. The company now offers its numerous customers a broad spectrum of high-quality DNA/RNA oligonucleotides for research, drug development and molecular diagnostics.

In 1992, the company decided to enter the field of DNA sequencing. Today, the company is very well positioned in this field and can offer its customers both traditional Sanger sequencing services and state-of-the-art next generation sequencing services. The establishment of addtional Sanger sequencing laboratories in Austria (Microsynth Austria GmbH in 2012) and Germany (Microsynth Seqlab GmbH in 2013) has helped to better access key European markets.
In the last two decades, sequencing has been complemented by various other specialized DNA/RNA-related areas such as nucleic acid isolation, PCR & qPCR & digital PCR, genotyping and bioinformatics. Through the acquisition of Ecogenics GmbH (microsatellite marker development and related genotyping services), Microsynth was able to expand its methodological repertoire and gain access to new customer segments (ecologists, breeders, botanists and zoologists).

The third and most recent department (Contract Research/Outsourcing) combines Microsynth's state-of-the-art portfolio in nucleic acid synthesis, sequencing and analysis to establish tailor-made analysis pipelines for customer projects. Through the successful execution of various projects with customers in the clinical or regulated environment in the recent past, decisive regulatory and project-related competencies have been developed. Today, Microsynth is a proven CRO offering GLP/GMP-compliant assay development, validation and sampling to support the development and production of drugs worldwide.

1989	The company is founded in Zurich as an ETH spin-off
1992	Entry into the Sanger DNA sequencing business
1994	Relocation to Balgach into own Microsynth building
1998	Establishment of qPCR & genotyping labs
2004	Headquarters extented by 2'000 m² lab & office space, launch of RNA synthesis
2007	Entry into the NGS sequencing business
2010	Own DNA/RNA isolation department is built up
2011	Takeover of the genotyping services from ecogenics GmbH, Switzerland
2012	Foundation of Microsynth Austria GmbH
2013	Merger with Seqlab GmbH in Germany Pilot Scale DNA/RNA Synthesis
2014	Handover of the executive management to Markus Schmid and Christof Wunderlin
2015	Official launch of CR/Outsourcing department
2016	Clinical research studies according to ICH guidelines
2017	Contract manufacturing of oligos for IVD and drug discovery
2018	Digital PCR technology is established
2019	30th anniversary is celebrated Headquarters extented by two floors

Microsynth ECOGENICS
Microsynth AUSTRIA
Microsynth SEQLAB

Our Mission

It is Microsynth's mission to be a leading service and solution provider for molecular biologists who require either high-quality DNA/RNA oligonucleotides, robust DNA/RNA sequencing & analysis solutions, or want to outsource project work.

Our Management

Dr. Tobias Schmidheini (center), founder of the company and Chairman of the Board, together with the two Co-CEOs, Christof Wunderlin (left) and Dr. Markus Schmid (right). Christof Wunderlin is responsible for Sales, Finance and Human Resources, while Dr. Markus Schmid is responsible for Operations and Quality Systems.
The members of the management determine Microsynth's strategy and have committed themselves to driving forward the internationalization and further growth of the company, while always acting in a sustainable and socially responsible manner.

Our Brand Promise

As a pioneer in our field, we have gained extensive critical know-how and experience related to DNA/RNA services since our incorporation in 1989. This expertise is our most valuable asset and we attach great importance to increasing our expertise through our commitment to technical competence, diligence and reliability. For more than three decades, our objective has been to serve our customers by delivering products and services of the highest quality, on time and with outstanding service – and all this at competitive prices. Last but not least, we are committed to sustainable development and to the protection of the natural resources of our planet.

DNA/RNA Expertise · Quality · Service · Sustainability

Our Locations

The **Microsynth AG** *headquarters in Balgach, Switzerland, where the company owns a 5-story building with an oligo production facility, analytic laboratories and offices of 2'800 m².*
ecogenics *is located at the headquarters.*

The industrial building at Leberstrasse 20 in Vienna. **Microsynth Austria** *is housed on the 4th floor.*

The industrial building at Maschmühlenweg 36 in Göttingen. **Microsynth Seqlab** *is housed on the 2nd floor, where it occupies state-of-the-art lab and office facilities.*

Quality System

Quality awareness is a prime concern to us. This includes the quality of all Microsynth products and services as well as the quality of all processes and procedures at Microsynth AG and its subsidiaries. Our constantly improving quality system is flexible enough to respond to the needs of different customers in different markets.

Microsynth AG is certified to **EN ISO 9001** and accredited according to **ISO/IEC 17025** (STS 0429) for Sanger sequencing, next generation sequencing and paternity testing. Microsynth's oligonucleotide synthesis facility is certified to **EN ISO 13485**, which is a formal recognition of our competence to produce, analyze and distribute nucleic acids, in-vitro diagnostic assays (IVD's) and applications. The company participates in proficiency tests. Proficiency tests are an important part of on-going qualification/validation.

Our Sanger sequencing laboratory holds the **GMP Compliance** issued by Swissmedic for manufacturing medical products including quality control (chemical, physical, biochemical and biological) of medical products as a contract laboratory.

The **Qualified Person** (QP) is in direct contact with relevant production coordinators on GxP issues and cooperates with production to ensure continuous improvement. The QP provides details on corrective actions required for batch deviations and assists in the implementation of quality systems within production to ensure compliance with GxP.

In addition, we are working according to the **EU Guidelines for Good Manufacturing Practice** (EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines / Arzneimittel-Bewilligungsverordnung (AMBV) and the ICH / PIC/S Guidance in GxP-projects (Contract Research)).

Company structure in terms of processes, interfaces and responsibility of resources are described in the **Quality Manual**. Process performance is monitored via **Key Performance Indicators (KPI)** and continuously improved via quality objectives and continuous improvement (KV). QMS relevant documentation and the associated records are managed in a controlled manner. This includes approval and release, identification, creation date and versioning. **Change management**, a **continuous improvement process** and **risk management** are implemented. Non-conformities / OOS are linked to a **CAPA process**. Customer complaints and deviations are recorded and brought into team meetings for training.

Processes are described in procedures and SOPs. They are reviewed periodically. We maintain a clean and hygienic manufacturing area. The processes are clearly defined, **validated** and controlled. Instruments are **qualified**. The requalification period is defined. Instrument-related test documents are archived. Changes that affect the quality are validated if necessary. In cases where the quality cannot be covered by verification, the production process is validated. Records demonstrate that all the steps required by the defined procedures and instructions are in fact taken. Deviations are investigated and documented. Records of manufacture that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form.

Operators are trained regularly in practical work and documentation procedures. New personnel are trained according to an introductory plan. This is documented in a dedicated dossier. If new functions are taken over, the pre-defined training/introduction must be attended.

Audits are performed to confirm that activities within the different processes correspond to internal and external demands, as well as to investigate the efficiency and suitability of the quality management system. By internal audits it is verified that the company policy is implemented throughout the entire organization. Supplier qualification is performed regularly.

Certification	Authority
EN ISO 9001	SQS (Swiss Association for Quality and Management Systems)
EN ISO 13485	SQS (Swiss Association for Quality and Management Systems)
ISO/IEC 17025	SSAS (Swiss Accreditation Service)
GMP	Swissmedic

Ecological Commitment

Microsynth and its subsidiaries (Microsynth Austria and Microsynth Seqlab) are committed to sustainable development[1] and the responsible use of finite resources. We are convinced that the sustainable way of working will be the foundation of our economic future.

At Microsynth we are committed to ecological behavior. The following examples illustrate the ecological commitment of Microsynth AG and its subsidiaries:

- The building of our headquarters in Balgach, Switzerland, represents a compact, well-insulated and airtight building according to Swiss Minergie standard. On the roof Microsynth operates a photovoltaic power system with an annual power output of roughly 18'000 kWh. The immediate environment has been shaped and ecologically enhanced by various structural elements (a. o. groups of trees and woody plants, stillwater areas, bat boxes) to match the needs and natural habitat of the animals.
- Wherever possible, we sort waste material for recycling and use the recycled products. Organic solvents needed for synthesis and analytic requirements are collected and eventually disposed in a safe and environmentally compliant manner
- Our printed materials are predominantly made from recycled fiber-based paper or FSC-certified paper. All marketing materials printed at external printing shops are printed climate-neutrally.
- Business travel is done (customer visits, congresses etc.) to a considerable part via train (within Switzerland and Austria nearby to 100%). Business trips via airplanes are extremely rare. Approximately 50% of our employees travel to their working place by cycle.
- Sequencing samples in Austria, Germany and Switzerland (where we operate sequencing facilities) are predominantly delivered via environmentally friendly transport vehicles (train, bicycle) to our labs. Only 20% of the covered distances are operated via (aircraft-managed) express courier services such as DHL or UPS.

Microsynth and its subsidiaries are constantly striving to achieve further improvements and optimizations in order to produce and analyze as sustainably as possible.
Our goal is to minimize resources and waste in our processes and workflows.

1) Sustainable development meets the needs of the present without compromising the ability of future generations to meet their own needs. This is the most frequently quoted definition for sustainable development. It is from "Our Common Future", also known as the Brundtland Report.

130 m² of solar panels capture the frequent sunlight of the St. Galler Rhine valley. This area is known for its above average number of sunny days within Switzerland.

Overnight sequencing of plasmids and PCR products has become a standard service in many European countries over the last couple of years. Usually, sequencing samples are collected by international courier companies and transported in aircrafts over large distances to centralized sequencing facilities. In contrast, in its core markets Microsynth operates decentralized sequencing facilities. This approach allows the company to rely on much more environmentally friendly courier systems with trains and bicycles as predominant transport vehicles.

Customer Support — We Are Here to Help

Microsynth and its subsidiaries stand behind each and every product and service offered, and take pride in offering the highest level of customer and technical support. We have a staff of highly-trained molecular biologists/ biochemists as well as administrative personnel ready to assist with any questions that you may have. If you have any question, please do not hesitate to call us!

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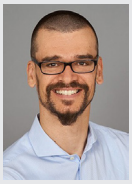
Your contact persons for technical questions:
Technical questions will be predominantly answered by Microsynth AG in Switzerland (for corresponding business areas and responsible persons see page 8).

Your contact person for sales questions:



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Microsynth Seqlab

Contact persons at Microsynth Seqlab can be found in the Microsynth Seqlab product catalog.

DNA/RNA Synthesis

Microsynth is a pioneer in the area of oligonucleotide synthesis and is proud to look back on more than 30 years of experience. This valuable know-how combined with the application of state-of-the art synthesizer technologies, purification as well as analytical systems allow us to produce a broad range of DNA/RNA oligonucleotides meeting the highest quality standards and requirements.

Microsynth's highly automated production systems ensure that you receive your oligonucleotides as needed. Further, an easy ordering system and our competent customer support will help to make your life easier.

General Featues and Benefits:

- **Stringent quality control** (online Trityl monitoring and MALDI-TOF MS or analytical PAGE)
- **Rapid turnaround time:** Synthesis scales up to 1 µmol of unmodified DNA oligonucleotides are shipped the next day
- **Standard modified oligos are shipped within 3 days**
- **Large range of synthesis scales** (yields from nmol to mmol are available)
- **Broad range of** 5'-, 3'- and internal **modifications**
- **4 different purity levels**
- **Very competitive pricing** for large quantity and/or prepaid orders
- **High guaranteed yields**
- **Trained scientists** with molecular biology background are happy **to support you** (from 8 am to 5 pm)!
- **Easy-to-use online portal** with a series of helpful tools (e.g. order tracking & history, convenient search and re-order option)

E.1 DNA Oligonucleotides

E.1.1 Unmodified DNA Oligonucleotides

Microsynth uses proprietary synthesizer technologies to offer oligonucleotides of highest quality. Our state-of-the-art production facilities and processes enable fast synthesis of unmodified DNA oligonucleotides in 4 different purity levels.

Desalted Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	13–60	2	10	8	40	1
0.04 µmol	13–80	3	15	9	45	1
0.2 µmol	6–150[4]	8	50	20	100	1
1.0 µmol	6–80	50	250	80	400	1
15 µmol	13–60	700	3'500	1'000	5'000	2

HPLC Purified Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	13–50	1	5	4	20	2
0.2 µmol	6–50[5]	3	15	7	35	2
1.0 µmol	6–50[5]	15	75	26	130	2
15 µmol	6–50	300	1'500	500	2'500	3

HPLC Purified & Dialysed Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	not available					
0.2 µmol	8–50[5]	3	15	6	30	3
1.0 µmol	8–50[5]	15	75	20	100	3
15 µmol	8–50	200	1'000	400	2'000	4

PAGE Purified Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	13–80	0.5	2.5	6	30	2
0.2 µmol	8–80 81 – 150[4]	2 0.5	10 2.5	8 4	40 20	3
1.0 µmol	8–80	7	35	20	100	3
15 µmol	not available					

1) The synthesis scale represents the initial amount of 3' nucleotides (starting material).

2) Guaranteed and average yields in OD are valid for unmodified oligonucleotides >20mer only.

3) Yields indicated in nmol represent an example calculation for a 20mer. For this calculation the following rule of thumb equation was applied: nmol of oligonucleotide = OD x 100/length of oligonucleotide. Please note that this calculation is based on sequences with virtually homogenous distribution of the 4 DNA nucleobases; it may vary for sequences with high GC contents >70% etc.

4) Oligos longer than 150 nt on request (we would like to discuss the proposed experiment/application with you beforehand in order to guarantee the best possible outcome)

5) On request up to 80 nt.

E.1.2 Modified DNA Oligonucleotides

Microsynth offers a wide variety of modifications (5′, 3′ and internal) for DNA oligonucleotides. The following 8 tables represent the most common modifications our customers usually ask for. If your desired modification or synthesis scale is not listed here, please contact us for availability.

Dyes

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.[1]**	**0.04[2]**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
AlexaFluor 350	X	X			X	X		X	X
AlexaFluor 430	X	X	X		X	X		X	X
ATTO 425/488/532/565/590/620	X	X		X	X	X		X	X
ATTO 550/647N	X	X	X		X	X		X	X
Cy3/Cy5	X	X	X		X	X		X	X[3]
Cy5.5/Cy7	X	X		X	X	X		X	X[3]
Methylene Blue (ATTO MB2)	X	X			X	X		X	X
Dyomics 510XL/530	X	X	X		X	X		X	X
Dyomics 630/681/781	X	X		X	X	X		X	X
FAM	X	X	X	X	X	X		X	X
HEX	X			X	X	X		X	X
JOE	X	X	X		X	X		X	X
ROX	X	X			X	X		X	X
TAMRA	X	X	X		X	X		X	X
TET	X			X	X	X		X	X
Texas Red	X				X	X		X	X
Yakima Yellow	X				X	X		X	X
California Red	X				X	X		X	X

1) Internal modifications are offered as dT compounds (e.g. ATTO550-dT). 2) 0.04 µmol synthesis scale is available for 5′ dyes only. 3) Available on request only.

Quenchers

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
BHQ-1 / BHQ-2		X	X[1]		X	X		X	X
Dabcyl		X			X	X		X	X
IQ-500			X		X	X		X	X
MGB-Q500		X			X	X		X	
MGB-Q530		X			X	X		X	

1) Internal BHQ-1/BHQ-2 are available as dT-compounds on request.

Bioactive Labels

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.[1]**	**0.04[2]**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
Biotin	X	X	X	X	X	X		X	X
Digoxigenin	X	X	X[3]		X	X		X	X
Cholesterol	X[4]	X			X	X		X	X
(GalNAc)3-Spacer12		X		X	X	X		X	X

1) Internal modifications are offered as dT-compounds (e.g. Biotin-dT). 2) 0.04 µmol synthesis scale is available for 5′ bioactive labels only. 3) Available with PAGE purification only. 4) Available on request only.

Functional Groups

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.[2]**	**0.04[1]**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
Alkyne (Click Chemistry)		X			X	X		X	X
Amino	X	X	X[2]	X	X	X	X	X	X
Azide	X	X	X[2]		X	X		X	X
DBCO (Cu-free Click Chemistry)	X	X	X[2]		X	X		X	X
Hexynyl (Click Chemistry)	X				X	X		X	X
Phosphate	X	X		X	X	X	X	X	X
Phosphorothioate (PTO)	X	X	X	X	X	X	X	X	X
Thiol	X	X			X	X		X	X

1) 0.04 µmol synthesis scale is available for 5′ functional groups only. 2) Internal modifications are offered as dT compounds (e.g. Amino-dT).

Nucleobase Modifications

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
2′-Deoxyinosine (INO)		X	X		X	X		X	X
2-Aminopurine			X	X	X	X	X	X	X
5-Me-dC			X		X	X		X	X
5-OH-Me-dC			X		X	X		X	X
Deoxyuridine			X		X	X		X	X
Mixed Bases			X	X	X	X	X	X	X
N6-Me-dA			X		X	X		X	X
Propynyl-dC			X		X	X		X	X
Propynyl-dU			X	X	X	X	X	X	X
TIPS-Alkyne-(C8)-dT[1]			X	X	X	X	X	X	X
TMS-Alkyne-(C8)-dT[1]			X		X	X		X	X

1) Available on request only.

Spacers

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
C3 Spacer		X	X		X	X		X	X
Spacer 18			X		X	X		X	X
Spacer C12			X		X	X		X	X
dSpacer (abasic site)			X		X	X		X	X

DNA/RNA Analogs

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5′**	**3′**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
2′-O-Methyl-RNA			X	X	X	X	X	X	X
2′-Methoxyethyl-RNA (MOE)			X	X	X	X	X	X	X
2′-Fluoro-RNA			X	X	X	X	X	X	X
LNA			X	X	X	X	X	X	X
S-cEt[1]			X	X	X	X	X	X	X

1) Available on request only.

Miscellaneous

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
2'-Deoxy-dA, dC, dG and dT[1]		X	X		X	X		X	X
Inverted dA, dC, dG and dT			X		X	X		X	X

1) 3'-Deoxy-dA, dC, dG and dT is equivalent to 2'3' dideoxyA/C/G/T.

E.1.3 Custom qPCR and Digital PCR Probes

Probe-based qPCR or digital PCR relies on the sequence–specific detection of a desired PCR product. Unlike dye-based methods that detect all double–stranded DNA, probe-based approaches utilize a fluorescent–labeled target-specific probe resulting in increased specificity and sensitivity. Therefore, use high-quality probes from Microsynth to improve the sensitivity and specificity of your qPCR or dPCR assay. Furthermore, benefit from various Tm enhancers (MGB, LNA etc.) or even combine them to tailor your assay to your individual needs.

Advantages:

- Possibility to adjust binding affinity via MGB, LNA and other Tm enhancers or even combine different Tm enhancers to tailor your assay
- Fast turnaround times: 3-5 business days
- Wide variety of fluorophore-quencher combinations
- Professional design service
- ISO 13485 certified production process
- qPCR & digital PCR assay development, validation, manufacturing and testing can be outsourced to Microsynth

Complementary Services:

- Assay validation via Microsynth's qPCR department

Fluorophores and Quenchers

Abs (nm)	Em (nm)	5' Dye	3' Quencher	Synthesis Scale		
				0.04	0.2	1.0
495	520	FAM	TAMRA, BHQ1	X	X	X
495	520	FAM[1]	iQ500-TAMRA, iQ500-BHQ1		X	X
521	536	TET	BHQ1	X	X	X
522	548	JOE	BHQ1		X	X
530	549	Yakima Yellow	BHQ1		X	X
535	556	HEX	BHQ1	X	X	X
546	563	Cy3	BHQ2	X	X	X
564	579	TAMRA	BHQ2		X	X
576	601	ROX	BHQ2		X	X
586	610	Texas Red	BHQ2		X	X
646	662	Cy 5	BHQ2	X	X	X
683	705	Cy 5.5	BHQ2	X	X	X
750	773	Cy7	BHQ2	X	X	X

Standard dyes and quenchers for dual-labeled probes (TaqMan, molecular beacons, LNA probes).

1) Double-quenched probes are currently only available with FAM as reporter dye.

Abs (nm)	Em (nm)	5' Dye	3' Quencher	Synthesis Scale		
				0.04	0.2	1.0
495	520	FAM	MGB-Q500	X	X	X
495	520	FAM	MGB-Q530		X	X
520	548	JOE	MGB-Q530	X	X	X
526	548	YYE	MGB-Q530	X	X	X
535	556	HEX	MGB-Q530	X	X	X

Standard dyes available for MGB probes at Microsynth.

E.1.4 Large Volume Orders

DNA Oligonucleotides - Large Volume Orders

Do you need large amounts of standard DNA oligonucleotides (≥100 oligonucleotides) per one single order or larger amounts of oligonucleotides with a certain modification? Depending on the number of oligonucleotides or modifications to be ordered, you will benefit from volume-dependent discounts.

Unmodified DNA Oligonucleotides — Large-Volume Orders[1]

# of DNA Oligonucleotides	Production Time [weeks]	Other Specifications	Price per Nucleotide
100–200	1	• synthesis scale: genomics or 0.04 µmol • length: 13–60 nt[2] • guaranteed yield[3]: 3 OD • purification: desalted • QC: MALDI-TOF or PAGE • delivery: in 96-/384-well plates or in single tubes; either dry or in solution (100 µM)	Want the best price possible? Then please contact us (info@microsynth.ch) and request your offer!
201–500	1–2		
501–1'000	1–2		
1'001–2'000	2		
2'001–5'000	2–4		
>5'001	>5		

1) Large-volume order means ≥100 oligonucleotides per one single order.

2) For oligonucleotides >60 nt please contact us.

3) Applies to unmodified oligonucleotides >20 nt.

Modified DNA Oligonucleotides — Large-Volume Orders

Significant discounts are possible if you need ≥10 modifications (e.g. NH_2, FAM or 5-Me-dC) of the same type per one single order or within a short time span. To profit from the best price possible, please contact us at Microsynth and request your offer!

Unmodified DNA Oligonucleotides — 1-Year Subscription Orders

In order to benefit from special conditions related to unmodified DNA oligonucleotides at low synthesis scales (genomics and 0.04 µmol scale), in general you have to fulfill two conditions:

1. Your annual volume/need is ≥100 oligonucleotides
2. You are prepared to purchase a certain amount of oligonucleotides within a 1-year period

Procedure: You estimate your annual need of oligonucleotides to your best knowledge → we make you an offer → you profit from the offered price upon your first order → should you be significantly below or above your estimate following 1 year, we would make you a new proposal.

E.2 RNA Oligonucleotides

E.2.1 Unmodified RNA Oligonucleotides

We utilize state-of-the art synthesizer and chemistry technologies in combination with various purification methods to offer you unmodified RNA oligonucleotides with 4 different purity levels:

Desalted Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	10–30	4	21	6	28	2
0.2 µmol	10–50[4]	8	35	10	45	2
1.0 µmol	10–50[4]	18	80	22	100	2
15 µmol	10–40	400	1'800	800	2'200	3

HPLC Purified Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	10–30	1	5	2	10	2
0.2 µmol	10–80	3	15	5	25	2
1.0 µmol	10–80	13	65	17	85	2
15 µmol	10–40	300	1'500	360	1'800	4

HPLC Purified & Dialysed Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	not available					
0.2 µmol	10–80	2	10	3	15	4
1.0 µmol	10–80	9	45	11	55	4
15 µmol	10–40	200	1'000	250	1'250	4

PAGE Purified Oligonucleotides

		Guaranteed Yield		Average Yield		Production
Synthesis Scale[1]	Length [nt]	[OD260][2]	[nmol][3]	[OD260][2]	[nmol][3]	Time [wd]
Genomics	not available					
0.04 µmol	not available					
0.2 µmol	10–50[4]	1	5	1	5	2
1.0 µmol	10–50[4]	6	30	7	30	2
15 µmol	not available					

1) The synthesis scale represents the initial amount of 3' nucleotides (starting material). 2) Guaranteed and average yields in OD are valid for unmodified oligonucleotides >20 and <40 nucleotides only. 3) Yields indicated in nmol represent an example calculation for a 20mer. For this calculation the following rule of thumb equation was applied: nmol of oligonucleotide = OD × 100/length of oligonucleotide (calculation is based on sequences with virtually homogenous distribution of the 4 RNA nucleobases). 4) Oligos longer than 50 RNA nucleotides can be produced in combination with HPLC purification.

E.2.2 Modified RNA Oligonucleotides

Microsynth offers a wide variety of modifications (5', 3' and internal) for RNA oligonucleotides. If your desired modifiction is not listed in the following tables, please contact us for availability.

Dyes

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
FAM [1]	X	X			X	X		X	X
Cy 3	X	X			X	X		X	
TAMRA [1]	X	X			X	X		X	X
Cy 5	X	X			X	X		X	
Cy 5.5	X	X			X	X		X	
Dyomics 681	X	X			X	X		X	
Cy 7	X	X			X	X		X	
Dyomics 781	X	X			X	X		X	

[1] 5' modification also available in 0.04 umol scale.

Quenchers

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
BHQ-1 / BHQ-2		X			X	X		X	X

Functional Groups

	Position			Synthesis Scale [µmol]			Purification		
Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
Amino	X	X	X	X	X	X	X	X	X
Phosphate	X	X		X	X	X	X	X	X
Phosphorothioate (PTO)			X	X	X	X	X	X	X

Nucleobase Modifications

	Position			Synthesis Scale [µmol]			Purification		
Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
RNA-Inosine (INO)		X	X		X	X		X	X
Deoxyuridine			X		X	X		X	X
Mixed Bases [1]			X		X	X		X	X

1) Available on request only.

Bioactive Labels

	Position			Synthesis Scale [µmol]			Purification		
Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
Biotin	X	X			X	X		X	X
Digoxigenin	X	X			X	X		X	X
Cholesterol	X	X			X	X		X	X

Spacers

	Position			Synthesis Scale [µmol]			Purification		
Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**DES**	**HPLC**	**PAGE**
C3 Spacer		X	X		X	X		X	X
dSpacer (abasic site)			X		X	X		X	X

DNA/RNA Analogs

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
2'-O-Methyl-RNA			X	X	X	X	X	X	X
2'-Methoxyethyl-RNA (MOE)			X	X	X	X	X	X	X
2'-Fluoro-RNA			X	X	X	X	X	X	X

Miscellaneous

	Position			Synthesis Scale [µmol]			Purification		
Type of Modification	**5'**	**3'**	**Int.**	**0.04**	**0.2**	**1.0**	**Des**	**HPLC**	**PAGE**
Inverted dA, dC, dG and dT			X		X	X		X	X

E.2.3 siRNA

siRNA, or small interfering ribonucleic acid, is a type of RNA that is involved in a number of biological processes, most notably RNA interference. RNA interference is a regulatory process that is used to control and limit the expression of specific genes. Regulatory active siRNA consists of annealed, complementary RNA sequences, usually 21-25 nucleotide in length and with symmetric 2 nucleotide 3' overhangs. Chemical synthesis enables the incorporation of DNA nucleotides as overhangs, thereby rendering the siRNA-duplex more stable against nuclease degradation.

Main Product Features and Benefits

- **Ready to use:** siRNA duplex annealed and dissolved in ready-to-use buffer (40 µM)
- **Two types of control siRNAs:**
  - Pre-synthesized control siRNAs
  - Scrambled siRNAs (Customized Negative Control siRNA)

Complementary Services:

- Modified siRNAs on request (e.g. GalNAc)
- Guaranteed knock down: if you use our free siRNA design service and let us produce ≥ 3 siRNAs, we guarantee that at least one of the synthesized siRNAs will reduce mRNA levels by at least 70%.

Microsynth supplies siRNA duplexes from standard (2x21-mers) to extended length (2x27-mers) at different levels of purity and scales, depending on the intended application:

- Desalted siRNA (for screening purposes)
- HPLC and PAGE purified siRNA (for screening and for use in cells)
- In vivo animal studies (on request)

	Desalted		HPLC		PAGE	
Synthesis Scale	**OD260**	**nmol**	**OD260**	**nmol**	**OD260**	**nmol**
0.04 µmol	9	21	4	8	not available	
0.2 µmol	16	35	7	16	2	5
Larger Scales	on request	on request	on request	on request	on request	on request

Classical siRNA duplexes (2x21-mers) have unit prices; if you need longer duplexes, each additional RNA base will be priced accordingly. Modified siRNAs are available upon request.

E.3 Special Synthesis Services

E.3.1 DNA Oligonucleotides for NGS Applications

Do you need NGS adaptors, fusion primers or any other specific primers for your next generation sequencing project? Due to our vast experience in the area of oligonucleotide synthesis (>30 years) as well as next generation sequencing (>10 years), Microsynth knows the exact quality requirements for NGS oligonucleotides. Therefore, you will be in good hands at Microsynth when requesting NGS oligonucleotides only, or equally when outsourcing your entire NGS project.

Main Product Features and Benefits:

- **High purity:** dedicated HPLC purifications up to 80mers for NGS applications[1]
- Availability of **current modifications** (5'-Phosphate, PTO, 5-Me-dC etc.)
- **Broad applicability:** recommended for any kind of NGS application and technology (e.g. Illumina, Ion Torrent, 454)
- Various delivery formats possible (dried, liquid, tubes, 96-well plates etc.)

Complementary Services:

- Analytical HPLC
- Certificate of Analysis
- Possibility to outsource the entire NGS project (from isolation to bioinformatics)

1) Here it is crucial to emphasize the importance of oligonucleotide purity for NGS applications. Most researchers take into account the n-x side products when they consider oligonucleotide purity, but do not ask their oligo suppliers for post-synthetic processes that have been optimized in terms of oligo cross-contamination arising from different customer orders. As a consequence many suppliers use cheaper high-throughput methods (e.g. Cartridge purification) to purify NGS oligonucleotides, which however is especially prone to cross-contamination. As a consequence, even a small amount of cross-contamination which is harmless in less sensitive applications (e.g. PCR or Sanger), may become a severe problem in the NGS data analysis since incorrect amplification products are likely to be sequenced as well. Therefore, Microsynth has established a specific process for production of NGS oligonucleotides that is based on a stringent HPLC purification procedure where the elimination of cross-contamination is given the highest priority.

E.3.2 Antisense Oligonucleotides

Oligonucleotides to be used in antisense experiments must be modified to increase their resistance against nucleases. There are several possibilities to stabilize oligos and to avoid enzymatic degradation during in vitro or in vivo applications. Microsynth can offer you the following types of modifications:

- **PTO (phosphorothioates) modifications:** PTOs contain one sulfur atom in place of an oxygen atom in the internucleotide linkage of DNA or RNA. This modification of the normal phosphodiester backbone is characterized by an increased cell uptake, high nuclease resistance and elicitation of RNAse H activity.
- **2'-O-Me-RNA modifications:** The incorporation of 2'-O-Methyl RNA nucleotides induces a resistance to a wide variety of nucleases, in particular RNase. Furthermore, 2'-OMe oligonucleotides show slightly increased affinity towards their complementary mRNA target sequence, thereby forming more stable hybrid duplexes compared to their non-modified DNA or RNA counterparts. This enables the formation of more stable hybrids with complementary RNA strands than would be the case for non-modified DNA and RNA sequences.
- **2'-MOE-RNA modifications:** Oligonucleotides incorporating 2'-O-methoxyethyl (MOE)-modified nucleotides can support most, if not all antisense mechanisms of action. Further key distinctive characteristics are nuclease resistance, lower toxicity, superior target binding specificity, as well as increased affinity towards complementary RNA. For more detailed information about 2'-MOE antisense oligonucleotides from Microsynth, please see the flyer on our website.
- **LNA modifications**: LNA containing oligonucleotides offer substantially increased affinity for its complementary strand, compared to traditional DNA or RNA oligonucleotides. This and the concomitant high nuclease resistance of LNAs results in unprecedented sensitivity and specificity and makes LNA oligonucleotides ideal for use in antisense applications.
- ***S*-cEt modifications**: cEt oligonucleotides (constrained ethyl nucleotides) are an advancement of LNA oligonucleotides. They have been developed for antisense applications and are mainly used in gapmers. Such ASOs show superior stability towards nuclease degradation compared to LNA without compromising binding selectivity or hybridization stability.
- **N-acetylgalactosamine (GalNAc)**: Conjugation of N-acetylgalactosamine (GalNAc) has become a major clinical strategy for delivery of oligonucleotides to hepatocytes (liver cells). Such conjugates are efficiently internalized by binding to the asialoglycoprotein receptor (ASGR), which exhibits high affinity for N-acetyl galactosamine terminated oligosaccharides.

	Position			Synthesis Scale [nmol]				Purification[1]
Modifications	5′	3′	Int.	0.04	0.2	1.0	15	HPLC + Dialysis
PTO			X	X	X	X	X	X
2′-O-Me-RNA	X	X	X	X	X	X	X	X
2′-MOE-RNA	X	X	X	X	X	X	X	X
S-cEt	X	X	X	X	X	X	X	X
LNA	X	X	X	X	X	X	X	X
(GalNAc)3-Spacer12		X			X	X	X	X

1) In case of in vitro and in vivo experiments we strongly recommend selecting HPLC followed by dialysis as purification in order to achieve physiological condition.

E.3.3 Click Chemistry

Click chemistry describes a thermodynamically favored reaction which enables quantitative and selective linkage of two different biomolecules. More precisely, the click reaction is a cycloaddition between an azide and an alkyne moiety either under copper-catalyzed or copper-free reaction conditions. The technology is reliable and stable which makes it an ideal oligonucleotide labeling method.

Characteristics of Click Chemistry:

- Reaction occurs in aqueous solution and at room temperature
- Stability toward H_2O, O_2, and most organic synthesis conditions
- Robust catalytic process
- No side reactions and lack of functional group interference
- Remarkable level of specificity for syntheses which require covalent linkage between two biochemical moieties.

Click Chemistry Modifications

	Position			Synthesis Scale [nmol]			Purification		
Modifications	5′	3′	Int.	0.04	0.2	1.0	Desalted	HPLC	PAGE
Azide-dT			X		X	X		X	X
3′ Alkyne		X			X	X		X	X
5′ Azide	X				X	X		X	X
3′ Azide		X			X	X		X	X
5′ DBCO	X				X	X		X	X
5′ Hexynyl	X				X	X		X	X

E.3.4 CRISPR/Cas Guide RNA

CRISPR/Cas has advanced to a standard technology in modern molecular biology and biotech labs in a very short time since its first publication in 2012. Briefly summarized: An endonuclease (Cas) is directed to a target DNA sequence using guiding RNA(s). The nuclease initiates a double strand break which leads to a knockout of the gene of interest. Basically every target can be made accessible for knocking out by this method. The easy programmability, the simplicity of the protocols and the stability of the system are clear advantages of CRISPR/Cas. Common experiments involving CRISPR/Cas are performed by cloning the Cas nuclease and the sgRNA into a plasmid for transcription and expression – this is no longer needed!

To further simplify your lab work, Microsynth offers you two ready-to-use guide RNAs (crRNA and tracrRNA) which – together with the Cas endonuclease – can directly be used in your experiment without any cloning steps.
The two guide RNAs have been optimized by including various types of chemical modifications resulting in an enhanced stability against nucleases. If compared with standard RNA, this prolongs the half-life of the guide RNAs in the cell and increases the success of your CRISPR/Cas experiment. High turnround for multiple target sites since you only need to design a new crRNA while you use the same tracrRNA. This and the various available nmol quantities make the Microsynth guide RNA's ideal for screening.

CRISPR Guide RNAs

crRNA	tracrRNA
chemically modified for increased half life	chemically modified for increased half life
Delivery yield: 2 nmol and 5 nmol	Delivery yield: ≥2 nmol
Larger scales on request	Larger scales on request
19 - 21 nt target sequence + 3 PAM sequence	Universally usable for all your experiments
PAGE purified for highest purity and efficacy	PAGE purified for highest purity and efficacy
100 % quality control	100 % quality control

E.3.5 Pilot Scale Production

Microsynth's production facilities can accommodate large scale oligonucleotide synthesis ranging from milligrams to tens of grams. Simply performing multiple conventional small scale solid-phase oligonucleotide syntheses would be inefficient and wasteful, requiring huge volumes and amounts of expensive solvents and reagents. Instead, we use specialized equipment and techniques for synthesis, purification and quality control of bulk amounts of oligos in order to match the demanding and specific needs of our customers.

Main Product Features and Benefits:

- **Scalable synthesis** range: from mg to gram quantities
- **Oligo sequences up to 30mers , longer oligos on request**
- **Available backbones:** DNA, RNA, MOE, LNA, 2'-OMe, PTO)
- **High purity:** stringent purification by HPLC available
- **Optional dialysis** of the product
- **Stringent quality control:** your oligo is verified using analytical HPLC/ LC-MS

Complementary Services:

- **High documentation standard:** Certificate of Analysis available
- Formulation, aliquotation, cation screening, endotoxin testing, chemical characterization etc.

Potential Applications:

- Manufacture of oligo components and/or mixtures for use in diagnostic kits
- Custom synthesis of therapeutically active oligonucleotides for drug discovery (ASOs, siRNA, aptamers, CpG oligos etc.)
- Biophysical experiments such as x-ray crystallography
- NMR studies

E.4 Optional Services

E.4.1 Purification

Desalted

All our oligos are at least desalted to largely remove residual low molecular by-products arising and accumulating from the frequent chemical reactions during synthesis. Such purification is sufficient for oligonucleotides shorter than 30 and/or oligonucleotides used for non-critical applications such as PCR, sequencing, probing, mobility shift or hybridization. However, desalted oligos are not recommended for use in molecular cloning projects.

Potential Applications:
1) PCR
2) DNA Sequencing
3) Probing
4) Mobility shift of hybridization

HPLC Purification

Oligos <50 bases in length can be well purified via reverse phase HPLC. Through this purification approach, preferably residual, n-x truncated oligos (lacking the hydrophobic DMT protection group at the 5'end) are removed. This results in a ≥85% purity of the targeted oligonucleotide. RP-HPLC is useful for a higher level of purity required for more demanding applications such as cloning, DNA fingerprinting, real-time PCR, FISH, etc.

Potential Applications:
1) Molecular cloning
2) DNA fingerprinting
3) Real-Time PCR
4) FISH

HPLC Purification & Dialysis

Dialysis as an add-on to HPLC is recommended if oligos need to be present in a physiological state. When performing in vivo experiments (e.g. in mice) this purity level is strongly recommended.

Potential Applications:
1) Antisense experiments
2) Cell culture studies
3) Physical chemistry and structure analysis

PAGE Purification

Polyacrylamide gel electrophoresis (PAGE) purification is generally necessary for long oligos (>50 bases) and for all those primers with critical 5' sequences (restriction endonuclease sites, RNA promoters). It is the best method to differentiate full-length oligos from aborted sequences (n-1 oligos), based on size, conformation and charge. PAGE purification has an excellent resolution and yields a product that is, on average, ≥95% pure. In this context, it is important to note that the purity level declines with increasing length of the oligonucleotide, and this is particularly true for oligos >120 bases. PAGE purification is highly recommended for sensitive experiments such as cloning, mutagenesis, DNA fingerprinting, in situ hybridization, gene synthesis, etc.

Potential Applications:
1) Molecular cloning
2) Mutagenesis
3) DNA fingerprinting
4) In situ hybridization
5) Gene synthesis

E.4.2 Hydration

DNA/RNA Oligonucleotides

Oligos are usually shipped in dry form. The dried DNA pellet becomes dislodged from the bottom of the tube during shipping and it can easily fly out of the tube when first opened, particularly as electrostatic attraction is present. For this reason: Always briefly centrifuge your oligos before opening for the first time, if you order oligos in dried format. If you want your oligos already delivered in liquid format[1] at the commonly used 100 µM concentration (100 nmol/ml), you can easily select this option at our online shop for a small surcharge. Should you prefer to receive your oligos solubilized at a specific concentration and/or in a specific buffer, let us know and we will deliver according to your specifications.

[1] DNA and RNA oligos are solved in water

siRNA

Our siRNAs are usually delivered ready-to-use: fully deprotected, sense and antisense strand already annealed and in liquid format[1] at 40 µM concentration. Should you prefer to receive your siRNA in dried format or solubilized with a specific concentration/buffer, let us know.

[1] siRNA is annealed in 10 mM Tris, pH 7.5, 20 mM NaCl

E.4.3 Customized Labels

Microsynth standard oligos are usually delivered in 2.0 ml tubes bearing a label with the oligo name, nucleotide sequence, order number, purification and production date. Should you wish a customized label in order to identify, sort and manage your tubes more conveniently, please let us know. Microsynth is quite flexible in designing labels that will meet your needs and are available for a small surcharge.

E.4.4 Mixing and Pooling

Preparing oligo mixes at the bench is usually a laborious and error-prone process due to manual handling. Whether you want to order a mixture of forward and reverse PCR primers or need a pool of hundreds or even thousands of oligos, Microsynth can help. Our automated liquid handling systems can handle the most complex mixing and pooling projects. Contact your sales manager with your needs, and he will consult you regarding the various possibilities and pricing.

E.4.4 Delivery in 2D Storage Tubes

When working with higher numbers of oligos, storage solutions ensuring sample traceability, sample security and optimal performance become increasingly important. Whether you need to securely store and keep track of hundreds or thousands of oligos, Microsynth can deliver your oligos in 2D barcoded storage tubes. Contact your sales manager with your ideas of implementing an optimized storage solution for your oligos, and he will consult you regarding the various possibilities and pricing.

E.5 Contract Manufacturing

E.5.1 Oligonucleotides for Use in IVD

Transitioning oligonucleotides from research to *in vitro* diagnostics (IVD) applications —where reagent quality may have an influence on critical medical decisions — involves a lot more than figuring out how to scale up production.
With over 25 years of experience in oligonucleotide synthesis and nucleic acid analytics, Microsynth has established itself as a reliable business partner for contract manufacturing of oligo components for in vitro diagnostic suppliers. Our state-of-the-art laboratories, superior quality reagents, stringent quality standards, and fully customizable manufacturing processes make Microsynth the partner of choice for diagnostic test manufacturers.
To learn more about how we can support you, please visit our website or get in contact with us using the contact form on that specific page.

E.5.2 Therapeutic Oligonucleotides

Several antisense oligonucleotide drugs have been approved by the regulatory agencies (FDA, EMEA) in the past two decades. Oligonucleotide-based therapeutics generally are a hot topic in research and development as they open the door for the treatment of a broad range of diseases that cannot be treated differently.

Two pioneers in the industry, Microsynth AG and Bachem AG, with long-term experience in catering to the phamaceutical industry as well as research organizations, offer the full portfolio of services and products needed to successfully develop, launch and market oligonucleotide APIs.

Microsynth AG, well known for 30 years of experience in the synthesis of modified oligonucleotides, is handling the early phase research and development projects, enabling clients to benefit from:

- a high level of expertise and experience in the synthesis of oligonucleotides (ASOs, gapmers, siRNAs) for drug discovery
- the best approach for the chemical synthesis using a broad portfolio of modifications (e.g. LNA, MOE)
- the fastest supply available, delivering products at exceptional speed
- sustainable and cost-efficient setup, from infrastructure to processes and systems
- fast, flexible and reliable service from quote to delivery

Benefits while working with us:
We guarantee

- coverage of the entire product development process, from R&D to commercialization
- fast and agile production in the early stages by Microsynth
- seamless transition of your project to Bachem
- priority access to GMP-manufacturing capabilities and resources
- no headaches for your CMC manager by working with the experts in the field
- best practice GMP standards and sound knowledge in API synthesis at all scales

DNA/RNA Analysis & Sequencing

With more than 25 years of experience in DNA Sanger sequencing, Microsynth has become one of the leading sequencing suppliers in Europe. Since 10 years Microsynth has also been active in next generation sequencing and has gained extensive knowledge in sequencing and bioinformatics. Beyond DNA sequencing, Microsynth has built up critical expertise in related analytical areas such as nucleic acids isolation, PCR (from classical PCR and qPCR to digital PCR) and genotyping (e.g. STR DNA profiling, genotyping by sequencing).

F.1 DNA/RNA Isolation

Microsynth relies on more than 16 years of experience in DNA/RNA isolation from different and difficult matrices like plant material, environmental samples or stool, etc. Our know-how in this area will help you to focus on the data analysis and interpretation rather than expending time and effort on optimizing your DNA/RNA isolation approach.

Each Microsynth nucleic acid isolation protocol includes the following four key factors:

1. Effective pre-isolation handling of the sample to allow high-yield nucleic acid isolation
2. Adequate choice of the isolation procedure specific for the matrix type
3. Validated workflow
4. Quality control of the isolated nucleic acids

The following table gives you an overview of the various matrices where we have solid experience in isolating DNA, RNA or plasmid DNA. We are also able to develop high-throughput isolation protocols for our customers due to our knowledge in laboratory automation.

Sample Matrix	Description
Industry Products	
Organic and Inorganic Chemical Products	Powders, liquids, gels, complex and demanding chemical composition
Biotechnological Products	Robust validated methods fit for purpose
Drug products	Raw material and finished products
Biological Fluids, Cells and Solid Tissues	
Cell Culture	Animal, supernatants (viral)
Animal Soft Tissues & Cells	Liver, brain, lung, heart, kidney, spleen
Animal Hard Tissues	Bones, teeth, shells
Animal Integumentary System	Feathers, hair, fin, etc.
Body Fluids	Blood, lymphocytes, plasma, urine, mucus, cerebrospinal fluid, saliva
Fixed Tissues	FFPE and glass-slide samples
Medical Samples	Ichor, collections and biobanks
Tough to Lyse	
Plants and Seeds	Fresh, dried and Herbarium samples
Fungi	Mycelium, fruiting body
Culture	Fungal, bacterial, archeal, supernatants (phage)
Environmental Samples	Biofilm, fecal, scat, soil (clay, loam, aquifer, sediments, potting soil, sand, sewer sludge, manure, compost, marine sediments), water
Plasmid DNA Purification	
E. Coli	Mini-, Midi-, Maxi-, Gigaprepscales, BAC, YAC, PAC plasmid
Yeast	Miniprepscale

F.2 DNA Sanger Sequencing

With more than 25 years of experience in DNA Sanger sequencing, Microsynth has become one of the leading sequencing suppliers in Europe. Microsynth is proud to offer its customers a high-quality Sanger sequencing service. By having established labs in Switzerland, Austria and Germany, we can offer this service with unmatched speed and environmentally friendly pickup service in those countries. Microsynth's decentralized approach results in shorter sample shipment distances and consequently the predominant use of bicycle/train-based courier logistics. With the Ecoli NightSeq®, Microsynth has developed an innovative new service for the sequencing of plasmids that does not require preps.

General Features and Benefits:

- **Read length** per run: **up to 1100 bases** or more in PHRED20 quality
- **Free sample shipment** via Microsynth drop boxes, if not available for your location, you can use our prepaid and pre-addressed envelopes for mail shipment
- Standard (>90) but also specific **primers** can be **added** to your sample **free of charge**
- Fast **in-house sequencing primer synthesis**
- Possibility to **fine-tune software analysis parameters** to achieve your desired performance
- **GC-treatment** for GC-rich templates or hairpin structures free of charge
- **Storage of primers up to 12 months**
- **Online archive** with 3 months of data access
- **Useful information for initial troubleshooting** is provided automatically for sequencing results that are difficult to sequence
- Direct access to **support by experienced academic staff**
- **Helpful online tools** enabling you to oversee your stock of labels and primers but also to share it among your group members
- **ISO 9001** and, on request, **ISO/IEC 17025 accredited** or **GMP sequencing**

A key feature of the Microsynth Sanger sequencing service is the great flexibility regarding the utilization, handling and storage of sequencing primers. The following table shows and describes the various primer sources which you can benefit from. Apart from "Order Now" and "Design at Microsynth", all other services are free of charge.

Name	Description
Premixed Primer	Primer added by customer.
Standard Primer List	Primer added by us (select your sequencing primer from a list of >90 standard primers which are stored at Microsynth).
Enclosed in Separate Tube	Primer added by us. Customer ships primer and DNA in separate tubes to Microsynth.
Stored at Microsynth	Primer added by us. Prerequisite for this option: You have already used the primer in the past. Your primer is stored for 6 months at our site.
Custom Primer List	Primer added by us. This option is an add-on to the option "Stored at Microsynth". If you know that a primer will be used frequently in future orders, send us a larger volume of this primer (at least 50 µl) and add it to your custom primer list. We will then store it for an extended period of time (up to one year).
Order Now	Primer added by us. Via this option you can order a new primer already during the order process. Microsynth produces your primer while your DNA is on the way to our sequencing lab.
Design at Microsynth	Primer added by us. This option is similar to "Order Now". In addition to the primer synthesis, we also perform the primer design. You only need to send us an email with a primer target sequence of 50–200 bases.

F.2.1 Single Tube Sequencing

Service-Specific Features for Single Tube Sequencing in Overview

Service Features	Economy Run		Ecoli NightSeq®		Premium Run / Primer Walking
Payment mode	prepaid	non-prepaid	prepaid	non-prepaid	non-prepaid
	Batches of 50 labels	per reaction	Batches of 50 labels	per reaction	per reaction
Upfront PCR purification possible[1]	X	X	not applicable	not applicable	X
Upfront DNA preparation of plasmids from *E. coli* possible[1]			included	included	X
Inspection of samples upon arrival and optimization of reaction conditions					X
Advanced treatment for difficult-to-sequence samples[1]	X	X			X
Access to special sequencing protocols for most challenging samples[1]					X
One-drop sequencing (for low sample amounts) & DNA extraction from agarose gels[1]					X
Multiple sequencing out of one tube possible[1]	upon request	upon request			X
Results delivery following sample receipt	MON-SAT	MON-SAT	MON-FRI	MON-FRI	MON-FRI
	before 8 AM next day[2]	before 8 AM next day[2]	before 2 PM next day[2]	before 2 PM next day[2]	next day
Data delivery via email possible	X	X	X	X	X
Re-run of failed reactions free of charge[3]	X	X	X	X	X
Extended technical support & troubleshooting					X
Sample storage	4 days	4 days	1 month	1 month	3 months

1) Additional charge possible

2) Applicable for purified samples only

3) In general, Microsynth automatically repeats failed sequencing reactions when an improvement potential is detected and the samples meet the sample requirements (concentration range). In addition, it is always possible to ask for specific repetitions of failed reactions (preferably by phone or e-mail).

Economy Run

Best-in-class Sanger sequencing service in 1.5 ml tubes for routine but also most difficult-to-sequence PCR products and plasmids. This service is available in a prepaid and non-prepaid version.

Main Service Features and Benefits:
See page 26 as well as table above.

Sample Requirements

General Information

DNA samples and sequencing primers can be sent premixed (within one tube) or separately (different tubes). Each DNA sample should have **a volume of 12 µl**. In case you wish that Microsynth adds your sequencing primer, please make sure that you send us sufficient amounts of your primer solution (minimally 20 µl of a 10 µM solution; in case you want to store your primer at our lab, consider that each sequencing reaction consumes about 3 µl). DNA samples and primers for sequencing reactions are preferentially dissolved in pure water. Alternatively, 10 mM Tris-HCl (pH 8) with a maximum of 0.01 mM EDTA can be used for a better long-term DNA stability. Standard TE-buffer is not suitable, because higher EDTA concentrations inhibit polymerase activity. Your templates will be stored for 4 days whereas your specific sequencing primers will be kept at our sequencing lab for at least 6 months (or for 12 months in case you have added them to your "Custom Primer List").

Sample Amounts and Concentrations

DNA Template	Concentration	Pipetting Scheme for Premixed Option
Plasmid[1]	40–100 ng/µl	12 µl DNA template solution + 3 µl sequencing primer solution (20µM)[3]
PCR Products[2]	**General Rule:** 1.5 ng/µl per 100 bp	
Length 100 - 400 bp	2 - 6 ng/µl	
Length 401 - 900 bp	4 - 17 ng/µl	
Length 901 - 2000 bp	12 - 70 ng/µl	
Primer (premixed)	4 pmol/µl = 4 µM	
Primer (separate)	10 pmol/µl = 10 µM	

1) Optimal plasmid concentration is 80 ng/µl

2) Regardless of whether the PCR is purified or non-purified

3) The addition of 3 µl of a 20 µM primer solution instead of a 10 µM primer solution to 12 µl DNA template solution (premixed option) usually leads to more robust sequencing results

Overnight Sequencing

Customers in Switzerland, Germany and Austria with direct access to a Microsynth drop box may benefit from our overnight sequencing service. Samples are processed overnight and results are ready for download before 8 AM in the morning of the next working day (you will be informed by email once your results are available). Please contact us in order to find out if an overnight service is possible for your location. As a registered customer you will find the information under Options & Preferences, Show Nearest Collection Points on the webshop.

Ecoli NightSeq®

Innovative new Sanger sequencing service in 1.5 ml tubes for plasmids. Drop your *E. coli* colonies into a Microsynth drop box, receive your result the next working day before 2 pm and accelerate your research by one day.

New Standard in *E. coli* Sequencing:

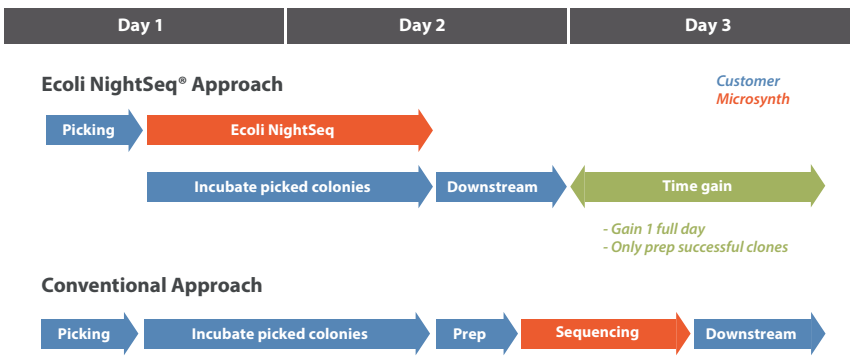
Game-changing new service from Microsynth. Save handling time in the lab and significantly reduce your expenditures on plasmid DNA purification kits by only isolating plasmids from clones showing the desired sequencing result. Get results with greater robustness.

Overnight Sequencing

Customers in Switzerland and Germany with direct access to a Microsynth drop box may benefit from our overnight sequencing service. Please contact us to find out if an overnight service is possible for your location.

Main Service Features and Benefits.

See page 26 as well as table at the top of page 27.



Comparison of the conventional with the new Ecoli NightSeq® approach. Send us your E. Coli colonies directly. After receiving the sequencing results, isolate only the plasmids from relevant clones and win one extra day.

Sample Requirements

Grow your *E. coli* on agar plates long enough to have a colony diameter of at least 1 mm. This will ensure a high cell density and is a prerequisite for reliable sequencing. Use a toothpick or something similar to take as much as possible of the *E. coli* colony and inoculate it into our tube. Use the same toothpick to inoculate your masterplate or a liquid culture which can be used straight away for your downstream process as soon as you get the sequencing results.

Premium Run

Looking for a personalized sequencing service that includes comprehensive customer support and troubleshooting? Need a top-quality sequencing service that is able to decode even difficult sequences? Then we recommend taking a closer look at our Premium Run Service.

Main Service Features and Benefits:

See page 26 as well as table at the top of page 27.

Sample Requirements

General Information

Each DNA sample and each primer must have a **minimum volume of 20 µl**. DNA samples and primers for sequencing reactions are preferentially dissolved in pure water. Alternatively, 10 mM Tris-HCl (pH 8) with a maximum of 0.01 mM EDTA can be used for a better long-term DNA stability. Standard TE-buffer is not suitable, because higher EDTA concentrations inhibit sequencing polymerase activity. Your templates will be stored for 3 months, whereas your specific sequencing primers will be kept at our sequencing lab for at least 6 months (or for 12 months in case you have added them to your "Custom Primer List".)

Sample Amounts per Sequencing Reaction and Concentration

Same as for the Economy Run (see table on page 28).

F.2.2 Plate Sequencing

Service-Specific Features for Plate Sequencing in Overview

Service Features	Economy Run		Economy Run Plus	Ecoli NightSeq®	
Payment mode	prepaid	non-prepaid	prepaid	prepaid	non-prepaid
	per plate	per reaction	per plate	per plate	per reaction
Upfront PCR purification possible[1]		X[1]	included	not applicable	not applicable
Upfront DNA preparation of plasmids from *E. coli*		X[1]	included	included	included
Inspection of samples upon arrival and optimization of reaction conditions	X	X	X		
Multiple sequencing out of one well possible[1]	X	X	X	X	X
Results delivery following sample receipt	MON-SAT	MON-SAT	MON-SAT	MON-FRI	MON-FRI
	before 8 AM next day[2]	before 8 AM next day[2]	before 8 AM next day[2]	before 4 PM next day	before 4 PM next day
Sample storage	1 month	1 month	1 month	1 month	1 month
Colony picking from agar plates into high-throughput 96-well plates and generation of glycerol stocks[1]	X	X	X		
Higher-scale plasmid isolation (Midi/Maxi) from selected clones including shipment back to customer's lab[1]	X	X	X	X	X
Shipment of isolated plasmids back to customer's lab[1]	X	X	X		

1) Additional charge applicable

2) Applicable only for purified samples that arrive at our facility in the early morning (no overnight sequencing possible!)

Economy Run

Do you have relatively high numbers (≥ 24) of PCR products or plasmids that can or need to be sequenced in parallel? And furthermore, have you come to the conclusion that you want to do the purification yourself? Then we recommend our Economy Run for 96- and, on request, 384-well plates.

Main Service Features and Benefits:
See page 26 as well as the table above.

Sample Requirements
Please provide at least 10 µl/well in 96-well plates. See the table "Sample Amounts and Concentrations" on page 28 for information on sample and primer concentrations.

Economy Run Plus

Best-in-class Sanger sequencing service in 96-well plates for PCR products and plasmids. The Economy Run Plus includes plasmid isolation from *E. coli* or PCR purification. This prepaid service (per plate pricing) is very popular due to its excellent price-performance ratio.

Main Service Features and Benefits:
See page 26 as well as the table above.

Sample Requirements

Non-purified PCR Products

PCR reactions can be sent directly after PCR in their reaction buffer at room temperature (RT) in the barcoded 96-well plate. The only requirement is that you check the quality of the sample on an agarose gel (a random subset is sufficient; at least one sample per PCR primer pair) before shipment. To obtain optimal sequencing results, it is important that all samples are in the recommended concentration range.

***E. coli* Cells (for Isolation of Plasmids at our Laboratories)**

If you send us *E. coli* cells, we recommend that you ship them in the barcoded 96-well plate within Luria Broth (LB) medium (or similar) at RT. Please make sure that your cells are incubated in 130 µl medium (containing the appropriate antibiotics!) for at least 3-4 hours with gentle shaking at 37° C prior to shipping. If no shaker is available at your lab, please let us know. We then perform a longer incubation at our lab.

Ecoli NightSeq®

Innovative new Sanger sequencing service in 96-well plates for plasmids. Drop your *E. coli* colonies into a Microsynth drop box, receive your result the next working day before 4 pm and accelerate your research by one day.

Overnight Sequencing

Customers in Switzerland and Germany with direct access to a Microsynth or Microsynth Seqlab drop box may benefit from our overnight sequencing service. Please contact us to figure out if an overnight service is possible for your location.

Main Service Features and Benefits:

See page 26 as well as table on page 30.

Sample Requirements

Grow your *E. coli* on agar plates long enough to have a colony diameter of at least 1 mm. This will ensure a high cell density and is a prerequisite for reliable sequencing. Use a toothpick or something similar to take as much as possible of the *E. coli* colony and inoculate it into our plates. Use the same toothpick to inoculate your masterplate.

Ready-to-Load Run

Convenient and cost-effective Sanger sequencing service in 96-well plates for ready-to-load plates. This service is particularly suitable for customers who have a workflow in their lab for sample preparation, cycling and purification and just want to outsource the actual analysis.

Main Service Features and Benefits:

- Rapid turnaround time: sequencing time in the lab down to 3 h, depending on the amount of samples
- Very cost-effective Sanger sequencing service

Complementary Services:

- 96-well or 386-well plates can be provided upon request.

Sample Requirements:

Sample preparation, cycling and purification according to protocols from Applied Biosystems. Deliver samples dissolved in water or formamide in 96-well or 384-well reaction plates compatible with Applied Biosystems 3730xl devices.

F.2.3 Advanced Services

Primer Walking

Fast and comfortable Sanger sequencing service for DNA templates longer than 1'400 bases. By sequencing from both ends, we advance about 1600 base pairs per day.

- **Non-assembled Primer Walking (single-stranded or double-stranded)** Upon sequencing your template, you will receive the single sequences. Final assembly will have to be done at your end.
- **Assembled Primer Walking (single-stranded or double-stranded)** After sequencing your template, assembly of the single sequences will be completed quickly and accurately at Microsynth. You will receive an electronic version of the aligned sequence.
- **Primer Walking for Sequence Verification (double-stranded)** Your sequences will first be assembled at Microsynth and then verified with the original sequence you provide. Together with the individual sequences you will receive an electronic version of the aligned sequence as well as a report of discrepancies.

In general, your DNA template is sequenced by a series of primer walking reactions. Since we are able to produce the sequencing primers in-house, we achieve a high sequencing speed. If you choose the double-stranded service, each base is confirmed by two sequencing runs.

Main Service Features and Benefits for all Primer Walking Services

	Non-assembled		Assembled	
Parameter	**SS[1]**	**DS[2]**	**SS**	**DS**
Fast in-house design and synthesis of primers	X	X	X	X
Delivery of synthesized sequencing primers on request	X	X	X	X
Fast sequencing: up to 1600 base pairs per day* *faster when a reference sequence is available	X	X	X	X
Editing of sequences	X	X	X	X
Delivery of electronic files such as project data sheet including sequencing strategy, text files and chromatograms for each single reaction			X	X
Delivery of chromatograms for each single reaction	X	X	X	X
Accurate assembly of single sequences			X	X
Verification of an assembled sequence against its original sequence (upon request)[3]				X

1) SS stands for single-stranded.

2) DS stands for double-stranded.

3) When a reference sequence is provided, Microsynth offers verification of the double stranded assembled sequence.

Clone & Sequence

PCR amplification of heterogeneous biological samples results in a heterogeneous mixture of PCR products (e.g. ribosomal 16S PCR generated from stool or soil samples). In order to be able to sequence individual PCR products by DNA Sanger sequencing, it is first necessary to clone them. At Microsynth, we are able to perform the entire process of cloning and sequencing, no matter how many clones your sequencing project may require.

Beyond Sanger DNA sequencing, we are also able to offer you comprehensive next generation sequencing services. In general, a next generation sequencing approach allows to circumvent the cloning step and becomes more economical with increasing sample numbers and throughput requirements. Please contact us to figure out which approach best fits your needs.

Exon Sequencing & Mutation Detection

Are you interested in identifying (point) mutations in genes or exons with great accuracy on a nucleotide level? Then we recommend our Exon Sequencing & Mutation Detection Service.

Main Service Features and Benefits:

- Project management and consulting
- PCR amplification of exons
- Double-stranded sequencing of the resulting PCR products
- Mutation reports

F.2.4 GMP-Compliant DNA Sequencing

Established cGMP Sanger sequencing service[1] for release testing of regulated biological drugs as well as for validation of DNA-based diagnostic tests/devices for market clearance applications. Whether you wish to make a European or FDA-level submissions, Microsynth's quality system has been set up to meet the most stringent quality requirements from regulatory authorities worldwide.

Our GMP DNA sequencing service have been established to support our customers in the following areas:

- **GMP Biologics Lot Release:** Sanger sequencing is applied as QC for final lot release of plasmid DNA and viral products used for biologics manufacturing
- **DNA/RNA identity and stability studies:** Sanger sequencing is used for identity and stability tests of various cell banks, plasmids, viruses and vaccines
- **Genetic testing for preclinical and clinical testing:** Sanger sequencing is utilized as "Gold Standard" method to analyze clinical trial samples (e.g. for SNP detection) or to validate assays to be used in preclinical or clinical trials
- **Validation of in vitro DNA-based diagnostic assays:** Sanger sequencing is used as "Gold Standard" method to validate nucleic acid based diagnostic assays or devices for regulatory clearance.

1) The certificate of GMP compliance has been granted by Swissmedic and is restricted to DNA sequencing by the Sanger method.

Main Service Features and Benefits:

- **2-fold or 4-fold coverage** sequencing service available
- All analyses performed according to **GMP requirements**
- Extended **GMP project reporting**
- Each project is guided by a designated study director
- Fast turnover time due to in-house synthesis of primers
- Guaranteed accuracy of final data >99.999% per base
- Sequence verification against a known reference sequence including mutation detection or de novo sequencing
- Evaluation of each chromatogram
- Assembly of sequence data and detailed sequencing strategy reporting
- Quality assurance statement (ISO/IEC 17025 (STS 429) and GMP Swissmedic 18-1647)
- Archiving of samples and data for 10 years (longer times available on request)

F.3 Next Generation Sequencing

F.3.1 Overview and Key Application Areas

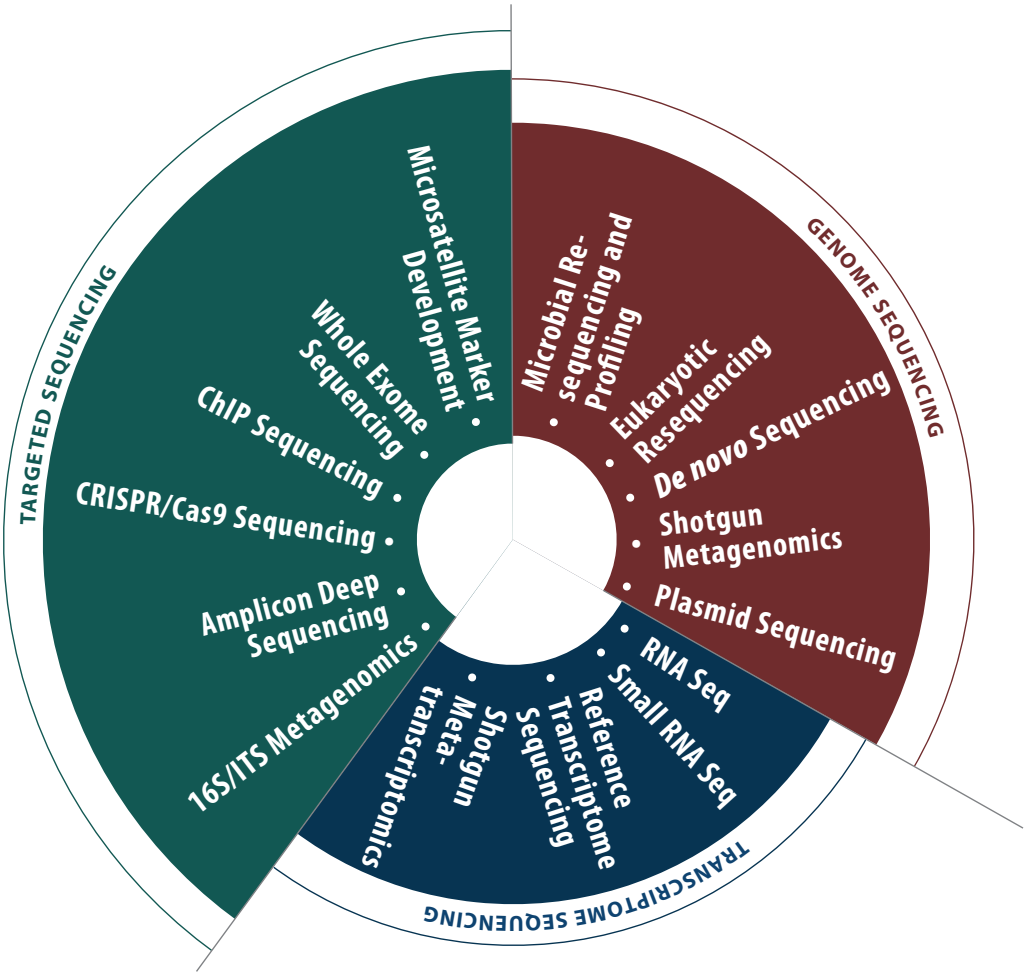
Microsynth can offer you a broad spectrum of applications in the area of next generation sequencing.

The image below gives you a rough overview of our NGS core domains. As NGS is still a very dynamic field, please do not hesitate to inquire about additional or customized applications. Focused on but not restricted to Illumina sequencing platforms and with a long-standing experience in SOLiD, 454 and PacBio sequencing, Microsynth is happy to advise you in picking the right strategy and technology for your application. Discussing your project with our NGS experts will help you to find the optimal approach for your project. Next generation sequencing at Microsynth means that you will get much more than the access to state-of-the-art NGS technologies. You can rely on our profound expertise and our more than 25 years of experience in DNA sequencing as well as related molecular biology knowledge such as DNA/RNA isolation, PCR/real-time PCR analysis and/or synthesis of DNA oligonucleotides.

In addition, you can expect extensive consultation during the entire phase of your NGS project. A study manager is interacting with you but also internally with a team of molecular biology experts and bioinformaticians to ensure that your project is optimally designed and carefully executed.

For analyzing your sequencing data, you can make use of our in-depth bioinformatics know-how and solutions, irrespective of the data source (whether data was generated by Microsynth or not).

Hence, your sequencing project will be in good hands at Microsynth and we do everything possible to deliver you high-quality results as basis for your further ongoing scientific work.



F.3.2 Project Consultation

The result and impact of a study depends on its experimental design. Therefore let our expert teams guide you in choosing the most suitable technological setup and accompany your experiment with knowhow to make it a success. If your project involves our bioinformatics services, our experts will guide you through the results and ensure that you get the most out of the data gathered.

F.3.3 Library Preparation and Sequencing

Depending on the requirements of your project, the DNA/RNA input material is prepared with the most suitable protocol and sequencing is performed on one of our Illumina MiSeq or NextSeq 500 NGS platforms which support high read throughput and variable read lengths. If very long reads are required to close gaps in bacterial genomes or to sequence full length 16S amplicons for instance then PacBio sequencing may also be offered. Check the table on page 37 to learn more about the short turnaround times of Microsynth.

F.3.4 Bioinformatics Analysis

Microsynth bioinformatics services are divided into stand-alone and complementary service modules. The latter offer valuable additional information to the stand-alone services, especially in a given experimental context (e.g. comparative analysis). Besides these standard service modules we also offer fully customized bioinformatics solutions. Our in-house team of highly experienced bioinformatics experts develop modules to satisfy your needs. All our service modules may also be applied on sequencing data obtained elsewhere. Microsynth uses community accepted, peer-reviewed open source software whereever possible. Standard data formats are utilized to facilitate publication, to enable downstream analysis and further deployment and long-term usability of the data. Essential results are presented as an interactive and user-friendly HTML report to guide you through the data. As a consequence, our bioinformatics services spare you laborious low level data handling, parametrization, necessary computational power and in turn provides you with state-of-the-art bioinformatics expertise to handle NGS projects in a professional manner.

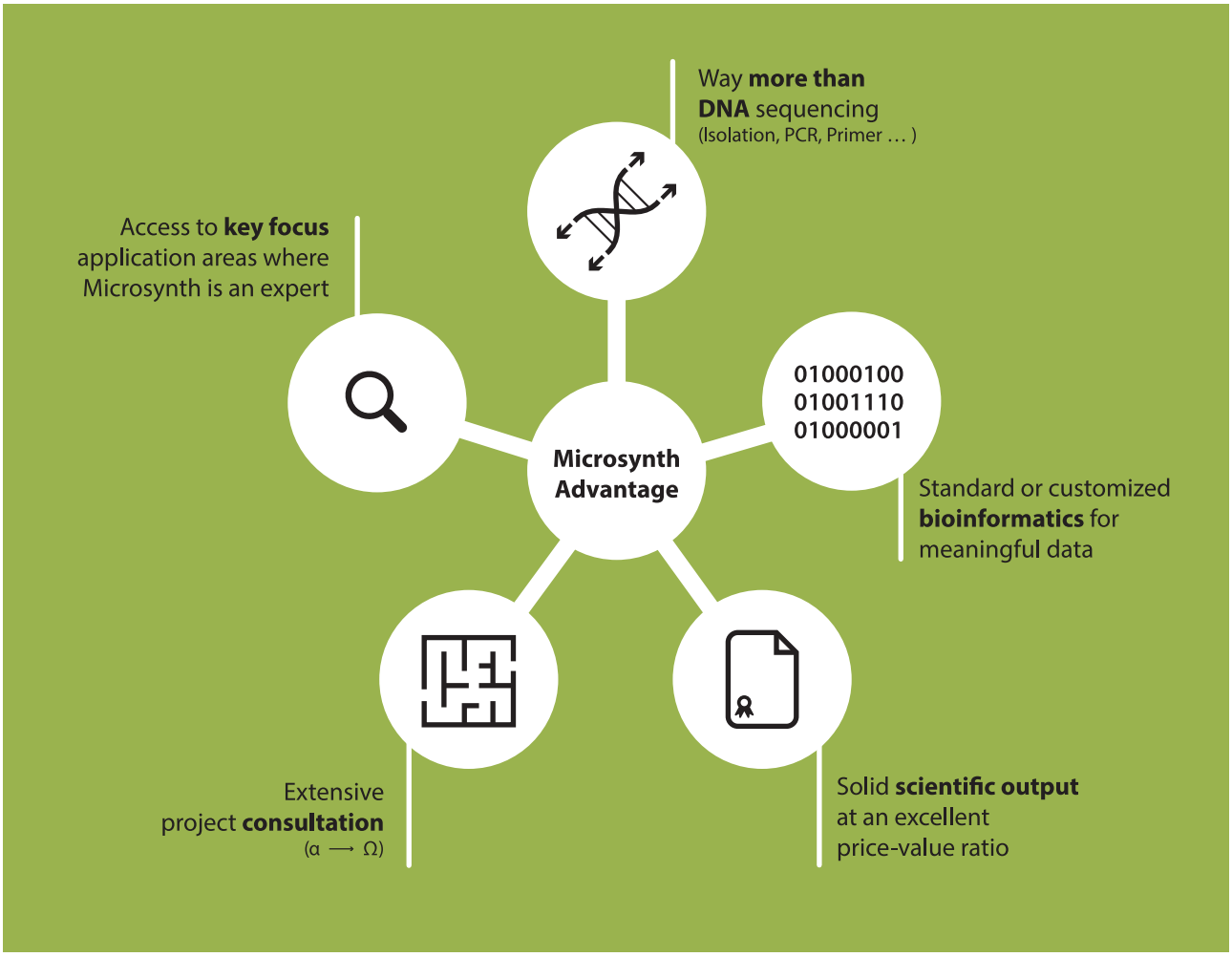
F.3.5 Complementary Services

Make use of the synergy we provide with our profound know-how and diverse technology portfolio. For instance, you may verify Microsynths NGS results by Microsynths Sanger sequencing.

Further Complementary Services:

- DNA/RNA isolation
- PCR, digital and qPCR services
- Synthesis of NGS primers

F.3.6 The Microsynth Advantage



F.3.7 Practical Information

Shipping Address
Microsynth AG
Next Generation Sequencing
Schützenstrasse 15
9436 Balgach
Switzerland

Shipment Recommendations
We recommend shipping the samples at ambient temperature/with ice pack (gDNA and PCR products) or frozen on dry ice (RNA). Please use properly sealed 96-well plates for larger sample amounts (more information on our website).

Buffer Recommendations
DNA: 10 mM Tris-HCl buffer (pH 7.5–8.5)
RNA: 10 mM Tris-HCl buffer (pH 7.0)

Sample Amounts Required for Illumina Sequencing

Type of Library	Amount (µg)	Concentration (ng/µl)
DNA for Nextera XT library*	>0.2	>10
DNA for TruSeq library	>0.5	>10
DNA for Whole Exome Sequencing	>0.5	>10
RNA for RNASeq library (poly(A) enriched)	>1	>20
RNA for RNASeq library (ribo depletion)	>3	>20
DNA for amplicon preparation (e.g. 16s rDNA or ITS analysis)	>0.1	>05
1st or 2nd step Nextera PCR product	>0.2	>05
Ready-to-sequence amplicon library *	>0.2	>10
ChIP-Seq libraries (req. ChIP DNA)	>0.05	>05
miRNA/small RNA (req. total RNA)	>3	>200
low input RNA (req. total RNA)	>0.01	>01

* *for single samples to be pooled >50 ng and >5 ng/µl per sample*

Sample Amounts Required for PacBio Sequencing

Type of Library	Amount (µg)	Concentration (ng/µl)
DNA Library	>10	>300

DNA/RNA Quantification

DNA/RNA quantification is recommended to be done by a fluorometric method, e.g. PicoGreen®, RiboGreen®, Qubit® etc.

DNA Quality Control

On each received sample, Microsynth performs a complete quality control prior to further sequencing steps. However, we do recommend that you also check your DNA on a gel or on the Bioanalyzer to allow a straightforward approach for your sequencing project. If you do so, please provide us with the gel picture or trace file as well.

Turnaround Times for Different Applications (Illumina Sequencing)

Service	Service Group	Turnaround Times in Weeks Library Preparation /Sequencing/ Bioinformatics
Microbial Resequencing and Profiling	Genome Sequencing	2/2/1
Eukaryotic Resequencing	Genome Sequencing	2/2/2
De Novo Sequencing	Genome Sequencing	2/2/3
Shotgun Metagenomics	Genome Sequencing	3/2/3
Plasmid Sequencing	Genome Sequencing	2/2/1
RNA Sequencing	Transcriptome Sequencing	3/2/1
Small RNA Sequencing	Transcriptome Sequencing	3/2/2
Reference Transcriptome Sequencing	Transcriptome Sequencing	4/2/2
Shotgun Metatranscriptomics	Transcriptome Sequencing	3/2/3
16S/ITS Metagenomics	Targeted Sequencing	2/2/1
Amplicon Deep Sequencing	Targeted Sequencing	3/2/2
CRISPR/Cas9 Sequencing	Targeted Sequencing	3/2/2
ChIP Sequencing	Targeted Sequencing	3/2/2
Whole Exome Sequencing	Targeted Sequencing	on request

Express service possible on request.

F.4 Digital PCR and Real-Time PCR

Microsynth, a leading provider of molecular biology services, offers a broad range of PCR services and products. More than 20 years of experience with customer projects of any size, our in-depth understanding of DNA/RNA quantification and our in-house production facility for oligonucleotides qualify Microsynth as your partner of choice for the development and validation of qPCR and digital PCR assays. Microsynth is also a competent and reliable partner for the subsequent performance of biological analyses, regardless of scale.

For further information, see **G5 Contract Research / Outsourcing** (pages 43 - 46).

F.4.1 qPCR/dPCR Assay Development

With Microsynth, you can order your **customized** and **MIQE-compliant qPCR** or **digital PCR assay** at very attractive prices and unbeatable delivery times.

Main Features and Benefits:

- Strong experience in digital PCR and qPCR assay design and validation
- High quality: Real-time and digital PCR assays with proven functionality due to comprehensive testing using a specific positive control as well as a no template control
- Optimal functionality: we design, synthesize and test your primer set(s) for their PCR performance
- Cost effective
- Easy publishing due to compliance with MIQE guidelines (full transparency with respect to sequence information of used primer and probes)
- Very fast delivery: You will receive your functional singleplex PCR assay within 1-3 weeks after the order.

Potential Applications:

Applications including absolute quantification, relative quantification, SNP genotyping, and presence/absence tests.

Available Assay Types:

Assay Type	Deliverables
Singleplex TaqMan qPCR Assays	Lyophilized probe & primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex SYBR Green qPCR Assays	Primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex TaqMan digital PCR Assays	Lyophilized probe & primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Singleplex EvaGreen digital PCR Assays	Primer pair (>1000 reactions); Positive control; All information regarding sequence, scale, purification and yield
Multiplex Assays	Subject to agreement between customer and Microsynth

F.4.2 Assay Validation

The Microsynth team has more than two decades of experience in validating assays. According to your requirements, we develop reliable, fit-for-purpose methods in a cost-effective manner to validate your assay. The validation is performed in compliance with appropriate regulations (e.g. ICH Q2(R1)) to assess accuracy, repeatability, intermediate precision, assay range, dilutional linearity and specificity.

F.4.3 Analysis Services

Microsynth offers competent project-based analysis services using real-time PCR and droplet digital PCR technology. All data is provided according to MIQE and digital MIQE guidelines.

Potential Applications:

- Absolute and relative quantification of the analyte
- Transgene copy number quantification
- Detection and quantification of the pathogens
- Detection and quantification of rare alleles
- microRNA analysis
- Genome editing detection and quantification
- Transgenic animal genotyping
- GMO testing
- Allergen testing
- Gene expression analysis
- SNP genotyping

F.4.4 qPCR and dPCR Food Testing Assays

Microsynth offers a well-chosen portfolio of advanced, cost-effective food testing kits. The range includes allergen-, species-, GMO- and microorganism-specific kits for qualitative and quantitative analysis.

Main Product Features and Benefits:

High quality: Ring-trial validated qPCR and digital PCR assays[1] (multiplex, quantitative, highly specific) with primer & probes manufactured inhouse by Microsynth
Attractive prices: for 5 x 20 qPCR or 5 x 10 digital PCR reactions
High efficiency: assays with up to 5 markers in one PCR run!
Convenient

- Easy-to-use kits with detailed instructions
- Compatibility with majority of qPCR systems

Potential Applications:

- Food quality and safety testing
- Allergen detection

1) Each assay has been fully validated and tested in interlaboratory ring trials. Assays are included in the Official Collections of Methods of Analysis of the Federal Office of Consumer Protection and Food Safety of Germany and of Switzerland as well as in the Scientific Opinion on the Evaluation of Allergenic Foods and Food Ingredients of the European Food Safety Authority. Food testing kits are supplied with the certificate of analysis from the federal food testing laboratory of Zurich.

Multiplex qPCR Kits for Animal Classification and Meat Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllMeat	Tetraplex	Chicken	Pork	Beef	Turkey	n.a.
AllHorse	Tetraplex	Sheep	Pork	Beef	Horse	n.a.
AllMilk	Tetraplex	Cow	Goat	Sheep	Water buffalo	n.a.
AllPaté	Pentaplex	Chicken	Duck	Goose	Turkey	Pork
AssignAnimal	Classification of animal species in combination with Sanger sequencing (cytochrome b)					
dNoBA	Digital PCR kit (EvaGreen duplex assay) for quantitative determination of non-basmati rice content in basmati rice.					

Multiplex qPCR Kits for GMO Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllGVOScB	Pentaplex	Nos Terminator	35S Promotor	Soy (lectin)	Maize (mhmg)	CaMV
AllGVOScC	Tetraplex	FMV Promotor	Bar gene	CP2/CP4/EPSPS	Pat Gene	n.a.
AllSoyA	Pentaplex	RoundupReady	Mon89788	Soy (Le1)	Soy2704	A5547-127
AllSoyB	Pentaplex	DP305423-1	DP356043-5	Lectin	CV127-9	Mon87701
AllSoyC	Pentaplex	Mon87708	Mon87769	Lectin	FG72	Mon87705
AllMaize C	Pentaplex	Starlink CBH	Mon863	T25	Maize (mhmg)	Mon810
AllMaize D	Pentaplex	Bt11	Nk603	Ly038	Maize (mhmg)	Bt176
AllMaize E	Pentaplex	GA21	DAS-59122-7	Mon89034	Maize (mhmg)	Mon88017
AllMaize F	Pentaplex	Syngenta3272	MIR604	TC1507	Maize (mhmg)	DP-98140
AllMaize G	Pentaplex	Mir162 Maize	DAS-40278-9	Mon87460	Maize (mhmg)	EventBt10

Multiplex qPCR Kits for Allergen Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllAll A	Tetraplex	Peanut	Celery	Soybean	Hazelnut	n.a.
AllAll B	Tetraplex	Cow's milk	Almond	Chicken egg	Sesame	n.a.
AllAll G	Tetraplex	Lupine	Almond	Brazil nut	Sesame	n.a.

Multiplex qPCR Kits for Bacteria Testing

Product Name	Assay Type	Marker 1	Marker 2	Marker 3	Marker 4	Marker 5
AllBakA IPC	Pentaplex	E. coli Stx1 Stx2 intimin	Salmonella (incl. bongori)	Listeria monocyto-genes	Campylobacter spp	IPC pUC19
AllCamp	Tetraplex	Campylobacter jejuni	Campylobacter lari	Campylobacter coli	IPC pUC19	n.a.
AllColi	Tetraplex	E. coli spp	E. coli eae/intimin	E. coli Stx1	E. coli Stx2	n.a.
AllBaktB	Pentaplex	E.coli	Clostridium per-fringens	Staphylococcus aureus	Bacillus cereus	IPC pUC19

F.5 Genotyping

Since 2003 Microsynth has been offering various routine as well as project-based genotyping services, especially those based on fragment length analysis of short tandem repeats (STR). Our solid experience in this area, our profound understanding of DNA/RNA isolation and lab automation as well as our in-house production facility for oligonucleotides qualify Microsynth as your partner of choice for a variety of genotyping questions.

F.5.1 Fragment Length Analysis

Comprehensive service packages for fragment length analyses including data analysis. Whether your application is a plain routine service or more complex R&D, Microsynth can offer you both the know-how and the necessary lab infrastructure.

Standard Fragment Length Analysis:
This service requires the customer to perform the PCR reaction and submit an aliquot of diluted, labeled PCR products. Microsynth will add the size standard and perform accurate separation of the fragments by capillary electrophoresis on an ABI 3730 XL system. The resulting data is provided by email as an FSA file.
Data analysis with GeneMarker software is available for a small surcharge. Reporting in form of an excel file includes:

- Allele calling (determination of allele name and bp size)
- JPEG exports of allele calling
- Additional information such as height, area, ratio and intensity of signals

Ready-to-load Fragment Length Analysis:
This service requires the customer to perform the PCR reaction and submit an aliquot of the labeled PCR products in size standard /HiDi formamide. Microsynth will perform accurate separation of the fragments by capillary electrophoresis on an ABI 3730 XL system. The resulting data is provided by email as an FSA file.

Data analysis with GeneMarker software is available for a small surcharge. Reporting in form of an excel file includes:

- Allele calling (determination of allele name and bp size)
- JPEG exports of allele calling
- Additional information such as height, area, ratio and intensity of signals

Customized Fragment Length Analysis:
Customized service from DNA isolation over PCR optimization to fragment analysis including reporting is available.

Since every project is different, please contact a Microsynth application specialist to discuss your project. Prior to contacting us, please ask yourself the following questions:

- DNA/RNA isolation to be outsourced? If yes, which kind of organism, tissue or source do you work with?
- Expected number of samples (single analysis, repeated analysis)?
- Delivery of samples (amount, quality and container)?
- Assay established? Single or multiplex assay?
- Number of controls to be included?
- Type of data needed (raw data, analyzed data, report)?
- Test samples available? Especially in case of larger projects, we prefer to perform initial testing in order to make a good bid.

Applications:
- Microsatellite (STR) Analysis
- DNA Fingerprinting
- SNP Genotyping
- Relative Fluorescence Quantitation
- Replacement of manual gel electrophoresis

F.5.2 Cell Line Authentication

ANNOUNCEMENT

Time to tackle cells' mistaken identity

The differences between a cow and a monkey are clear. It is easy to tell a moth from a mosquito. So why are there still scientific studies that mix them up? The answer is simple: hundreds of cell lines stored and used by modern laboratories have been wrongly identified. Some pig cells are labelled as coming from a chicken; cell lines advertised as human have been shown to contain material from hamsters, rats, mice and monkeys.

Nature/VOL 520 16 April 2015

Why Test Cell Lines?

It is a fact that cross-contamination and misidentification of mammalian cell cultures is widespread. An incredibly high percentage of 15–20% of all cell line-based biomedical research is affected by misidentified cell lines. Therefore, establishing a cell line's identity through STR profiling is essential to conducting valid and reproducible research. Moreover, more and more journals (not only the high-impact ones!) are requesting the authentication of cell lines as prerequisite for acceptance of manuscripts.

Microsynth has over 10 years of experience in genotyping and offers an easy-to-use service for human and mouse cell lines. Rely on our experience and make your research reliable!

Main Service Features and Benefits:

- **Easy sample handling:** Just send us your cell line at room temperature. Microsynth will isolate and genotype your cell lines and return an analysis report including electropherograms.
- **Easy sample shipment:** Just place the cell lines in one of our numerous collection boxes with daily pickup service in Germany, Austria or Switzerland. Alternatively send us the cell lines with your preferred postal service at room temperature.
- **Reliable results:** Microsynth has over 10 years of experience in genotyping, and your results are summarized in a meaningful analysis report.
- **Multiple organisms:** Currently a standard cell line typing service is offered for human and mouse cell lines. In cooperation with our subsidiary ecogenics GmbH, we can develop high-quality microsatellite markers for virtually any organisms. Contact us to discuss your specific needs!
- **Additional services** (available at an extra charge):
  - Database comparison of the DNA profile (ATCC, Microsynth in-house database)
  - Mycoplasma contamination testing of cell culture supernatant

How Does it Work?

- Collect 1.0-5.0 million cells and wash the cell pellet twice in PBS or another appropriate buffer. Resuspend cell pellet in 0.5 ml of 70–90% ethanol and transfer to 1.5 ml screw cap tube. If you want to send us isolated DNA, please provide ≥30 µl gDNA at a concentration ≥10 ng/µl in Tris or low-EDTA buffer (10 mM Tris, 0.1 mM EDTA). For mycoplasma testing, please send 100 µl of the culture supernatant directly.
- Download and fill out the order form (see our website). Send a copy to genotyping@microsynth.ch.
- Print the order form and put it together with the samples in a plastic bag or envelope. Drop the samples in the next Microsynth or Microsynth Seqlab collection box. To find the closest collection point, please login the webshop at www.microsynth.ch and click "Options & Preferences" under DNA Sequencing and find details under "Collection Points".
- Microsynth will confirm the receipt of your samples and ship back the analysis results within one week.

Further Reading

- *ATCC SDO Workgroup ASN-0002 (2010). Cell line misidentification: the beginning of the end. Nature Rev. Cancer 10:441–448.*
- *Barallon, R. et al (2010). Recommendation of short tandem repeat profiling for authenticating human cell lines, stem cells, and tissues. In Vitro Cell.Dev.Biol. – Animal 46:727–732.*
- *Chatterjee, R. (2007). Cases of Mistaken Identity. Science; 315 no. 5814:928–931*
- *Almeida, J. et al (2013). Mouse cell line authentication. Cytotechnology 66: 133–147.*
- *Yu, M. et al. (2015). A resource for cell line authentication, annotation and quality control. Nature 520:307–311.*

F.6 Ecogenics

ecogenics GmbH is a subsidiary of Microsynth AG and has put its focus on microsatellite marker development and related genotyping services since its incorporation in 2001. Our commitment is to be the partner of choice for ecologists, breeders, botanists and zoologists looking to outsource DNA work.

From research project developments through routine analysis our protocols, based on state-of-the-art technologies, combined with our excellent project management allow rapid and successful accomplishment.

Together with our mother company we will find the best and most cost-effective solution for you. From project design to data analysis you can get everything from one source. Furthermore, after project completion we don't leave you alone, we provide our support with our know-how to make sure the data works for you.

F.6.1 Microsatellite Marker Development

The generation of SSR-enriched data by next generation sequencing allows straight-forward microsatellite development for any species within a short time span. We deliver well-characterized markers and provide you with all information needed to publish the markers in a primer note or in a public database. It is up to you, until which step of development you plan to involve ecogenics and whether you want to perform subsequent genotyping projects by yourselves or whether you wish to further collaborate with us.

F.6.2 Genotyping by Microsatellite Markers

For genotyping projects involving larger numbers of samples and markers, it is more cost effective to run multiplex PCR reactions compared to singleplex reactions. We can establish multiplex assays to the needed degree of complexity. We are happy to establish multiplex assays for markers developed by ecogenics or for markers published in scientific journals. If you are not sure if published markers run on your species or subspecies, we can include further initial tests to ensure that the markers perform stably on your samples. For markers developed and multiplexed by us, we offer free allele calling for further genotyping work done at ecogenics.

In order to ensure highest data quality and to speed up the progress of your research projects, we offer the full range of genotyping services. Our vast experience with DNA isolations from many sources, combined with our expertise in PCR, ensures optimal results. For fragment length analysis, we use Applied Biosystems 3730xl DNA Analyzer. Whether you wish to receive fluorescent trace files (.fsa) or also an allele table with all identified alleles per marker and sample is up to you to decide.

F.6.3 Genotyping by Sequencing (GBS)

With the rapid progress of next generation sequencing technologies, GBS became available to researchers and breeders for a very attractive price. We do not leave you alone with complex data sets, but can assist you through bioinformatics support. Furthermore, we are happy to support you with setup of robust library preparation protocols and sequencing strategies for GBS.

In contrast to more traditional genotyping methods, SNP genotyping by next generation sequencing does not require previous marker development or sequence information, but allows direct SNP genotyping within any population of interest at the desired marker density.

Contract Research/Outsourcing

In today's competitive environment, the pharmaceutical, biotech and life science industries as well as academic/public institutions are increasingly forced to reduce costs and become leaner. In other words, doing more R&D with less, and doing it smartly, has become the overriding strategy!

G.1 Expertise

Microsynth has accumulated comprehensive knowledge to translate the customer demand into a well-defined analytical procedure, taking advantage of a state-of-the art toolbox in DNA and RNA-based synthesis and analytical platforms, all operated in-house.

The first and most important step to design an efficient and successful analytical procedure is to fully understand the project both at the scientific level as well as in its regulatory context.

Notwithstanding the idiosyncratic features of a given project, it usually can be handled by a stereotypical approach, divided into distinct phases: (1) the research & development phase, (2) an optional validation phase, and finally, (3) the analysis of the samples.

After careful evaluation of the customer demand, the analysis strategy is defined as a sequence composed of modules from our comprehensive analysis toolbox: Sanger sequencing, digital PCR, real-time PCR, next generation sequencing, and dedicated bioinformatics solutions.

The laboratory work then starts with the research and development phase: different methods and parameters are explored and tested at a small scale to identify the successful approach. Depending on customer needs, the successfully developed analytical procedure can then be further validated - mandatory for analytical procedures used in the regulated environment.

Once the analytical procedure has been established, the customer's samples will be analyzed.

G.2 Working with Microsynth

In today's competitive environment, the pharmaceutical, life-science and biotech industries as well as academic and public institutions are driven to optimize their research and production to become faster and leaner in order to save costs. Thus, compared to diverting valuable internal resources to projects outside the core competence, outsourcing to a competent partner may be a more promising strategy for success. Outsourcing is also an attractive option to test an idea for its potential or to carry out routine procedures not worth establishing in-house. Microsynth has accumulated vast knowledge in designing and executing outsourcing services in the realm of RNA/DNA analytical procedures for diverse customers ranging from start-up biotechnology firms, large multinational pharmaceutical or nutritional companies, to university hospitals and scientific institutions.


Expertise & Know-how


Solution Driven


Quality

G.3 Technical Portfolio

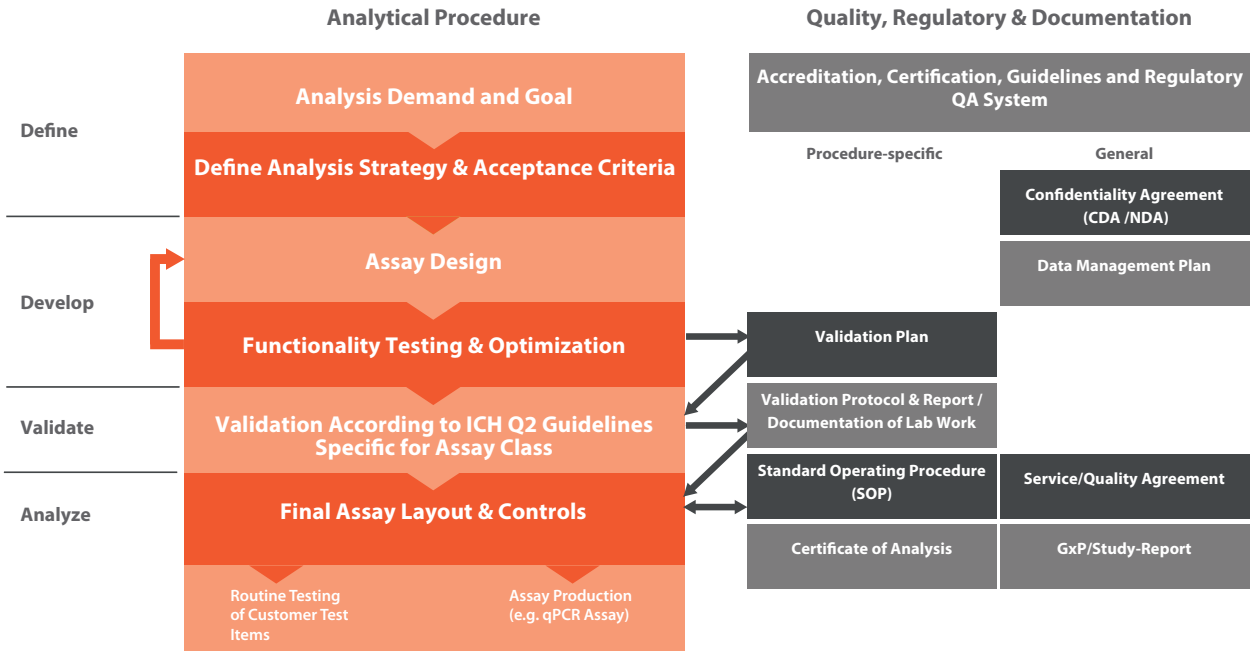
DNA/RNA is our world. Microsynth provides a broad portfolio for DNA/RNA-based analytics ranging from DNA/RNA isolation to bioinformatics analyses. Moreover, in-house DNA/RNA synthesis is available to complement the analytical portfolio.

G.4 Regulatory Expertise

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has defined the standards for the development and registration of medicines. In VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY (Q2R1), three major types of analytical procedures were defined: identification tests (for example a Class A assay showing that a particular personalized RNA vaccine has an identical sequence as expected), quantitative tests for specific DNA/RNA species (for example a Class Bq assay to quantify genome edits in CRISPR/CAS9 test items), and limit test for the control of impurities (for example a Class Bd assay demonstrating the absence of contaminating RNA/DNA species in a test item).

Microsynth has experience in the validation of all three types of analytical procedures. All validation tests require high-quality reference material, either provided by the customer or developed by Microsynth. Identification tests are typically straightforward, while quantitative tests for impurities' content and limit tests for the control of impurities usually require a development phase to establish the relevant assays.

The validation will result in a report that describes the final assay, the details of the analytical procedure and the standard operating procedure (SOP) for the specific analysis. Important information about control samples and standards used in each analysis round are also provided. This information is instrumental to evaluate whether data of each testing round is valid.



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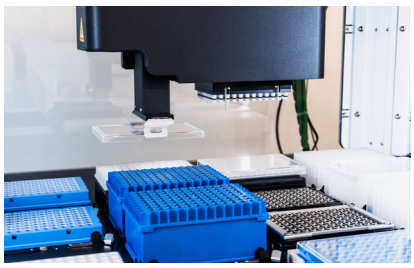
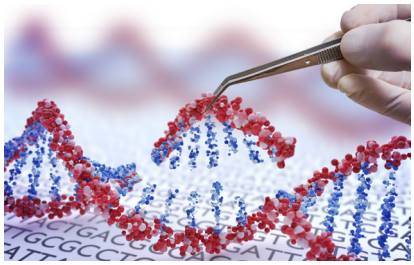
G.5 Possible Applications

Assay Development
- Development of molecular biology assays from target (e.g. companion animal diagnostics, IVD, GMO, etc.)
- Validaton of molecular biology assays according to ICH guidelines
- Cross-validation against a reference method



Biologics Testing
- Contamination and impurity testing
- Lot and final drug product release testing
- Cell line characterization
- Viral clearance studies



Gene Editing / Gene Therapy
- CRSPR editing analysis
- rAAV characterization
- Off-target analysis

For further information, please visit our website (www.microsynth.ch). Interested in discussing your contract research project with an expert or receiving an offer? Then get in contact with Bruno Müller (bruno.mueller@microsynth.ch).

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