U.S. FDA's Oversight of Intentional Genomic Alterations (IGAs) in Animals

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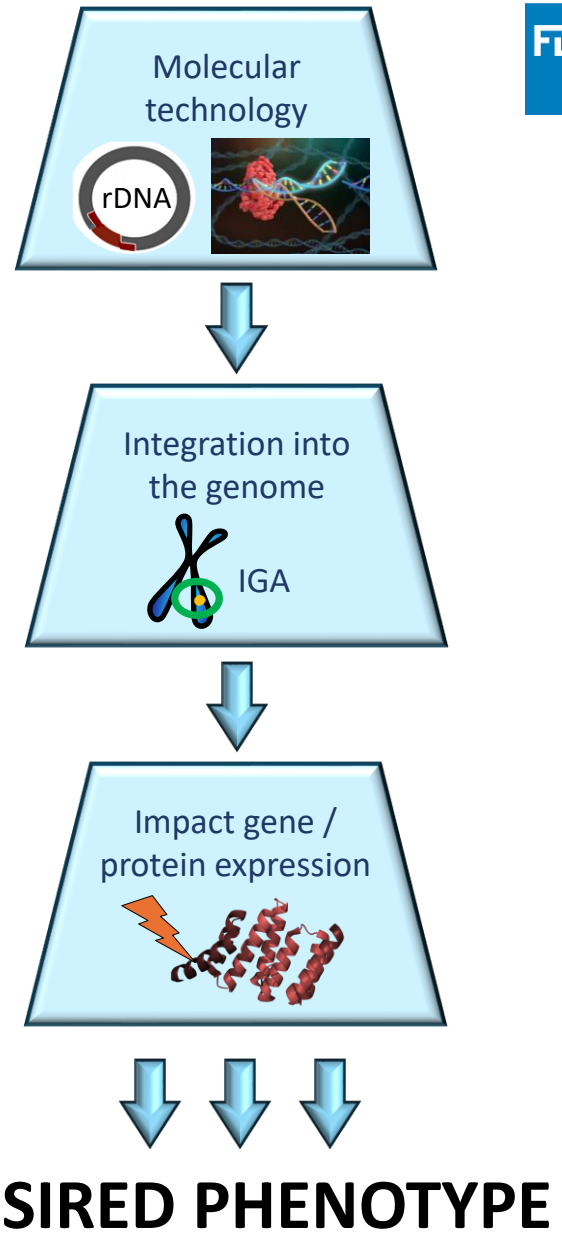
What is an intentional genomic alteration (IGA)?

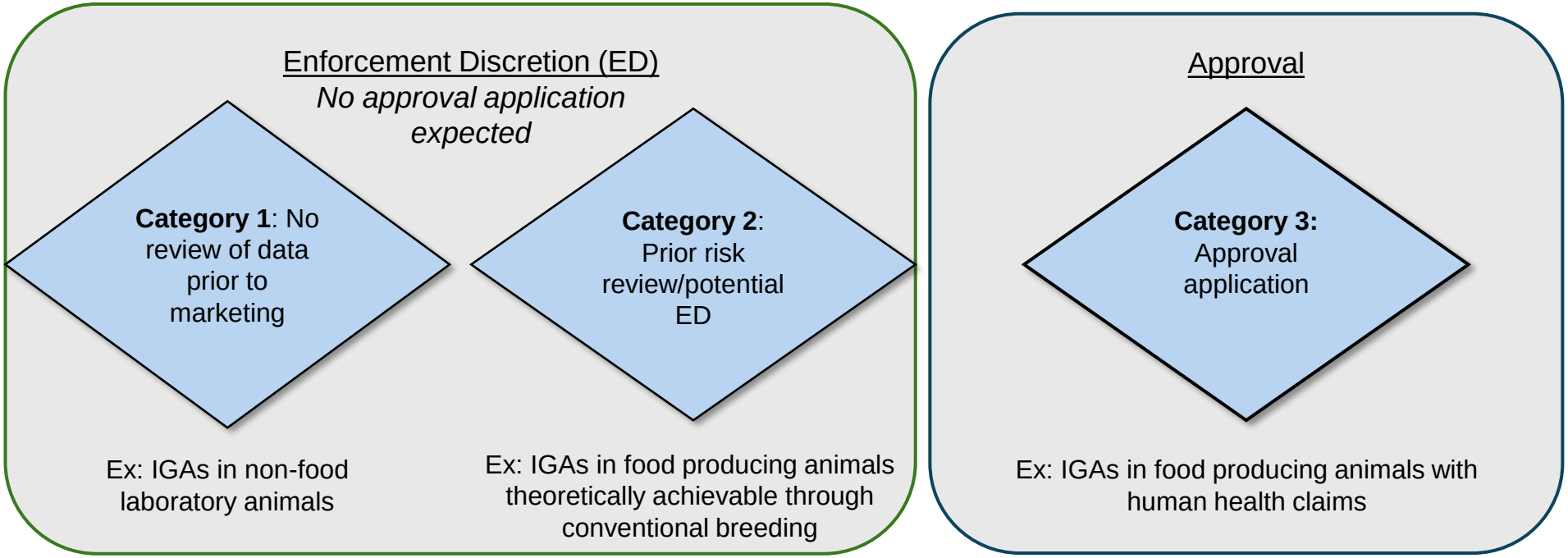
- An IGA is a change introduced into the animal's genome using molecular technologies (e.g., rDNA, CRISPR-Cas, TALENs, etc.).
- Includes random or targeted DNA sequence changes (e.g., nucleotide insertions, substitutions, or deletions).



Oversight Objective

- For FDA approval, developers of IGAs in animals must demonstrate
  - **Safety** to the animal
  - **Safety** to anyone who consumes food from the animal
  - **Effectiveness** (the IGA does what it is supposed to do)

Risk-based review of IGAs in Animals



*Described further in Guidance for Industry (GFI) #187A

Category 2: No application expected following prior review of risk factor data

- What are we determining?
  1. Understand product's risks
  2. Any identified risks are appropriately mitigated; and
  3. No further questions for which we would need to see additional data

- What are the types of IGAs that may fall under Category 2?
  1. Certain IGAs in animals intended for food-use:
     - History of safe use
     - Could theoretically be created with conventional breeding
  2. Other IGAs:
     - E.g., fluorescent aquarium fish; food-producing animals used as disease model organisms

Category 2: Risk considerations

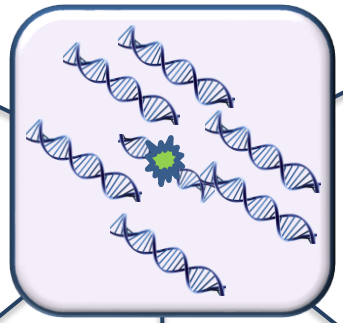
GFI 187A risk questions for IGAs in animals:

- Is there anything about the IGA itself that poses a human, animal, or environmental risk? For example, does it contain sequences that can cause human or animal disease either intrinsically or by recombination?
- For an unintentional environmental release or escape, does the animal with the IGA pose any more of an environmental risk than its counterpart with no IGA?
- Are there concerns over the disposition or disposal of animals with the IGA that could pose human, animal, or environmental risks?
- Are there are any other safety questions or risk issues?

Category 2: Basis for determination

Molecular characterization
- Experimental design
- Data to evaluate intended alteration & any unintended edits
- Method details for characterization & commercialization

Post-risk review/pre-marketing expectations
- List product
- Register establishment
- Reporting of changes & any other info outlined in the letter



Animal safety
- Health data
- Literature references
- Phenotype confirmation

Food safety
- Literature references
- Commitment not to introduce into the food supply (where warranted)

Impact on the environment
- Containment (where warranted)
- Facility information

Risk-Reviewed IGAs in animals under Category 2

IGAs in aquarium fish, intended to cause the fish to fluoresce

GloFish Red Danio RZF2005 RDNA construct in *Danio rerio*
GloFish Purple Danio PZF2010 RDNA construct in *Danio rerio*
GloFish Blue Danio BZF2010 RDNA construct in *Danio rerio*
GloFish Orange Danio YZF2010 RDNA construct in *Danio rerio*
GloFish Green Danio GD2006 RDNA construct in *Danio rerio*

GloFish Orange Tetra YT2012 RDNA construct in *Gymnocorymbus ternetzi*
GloFish Green Tetra GT2011 RDNA construct in *Gymnocorymbus ternetzi*
GloFish Pink Tetra RT2012A RDNA construct in *Gymnocorymbus ternetzi*
GloFish Red Tetra RT2013 RDNA construct in *Gymnocorymbus ternetzi*
GloFish Purple Tetra PT2013 RDNA construct in *Gymnocorymbus ternetzi*
GloFish Blue Tetra BT2014 RDNA construct in *Gymnocorymbus ternetzi*

GloFish Green Barb GB2011 RDNA construct in *Puntius tetrazona*
GloFish Red Barb RB2015 RDNA construct in *Puntius tetrazona*
GloFish Purple Barb PB2019 RDNA construct in *Puntius tetrazona*
GloFish Orange Barb OB2019 RDNA construct in *Puntius tetrazona*

GloFish Orange Shark OS2016 RDNA construct in *Epalzeorhynchos frenatus*
GloFish Purple Shark PS2016 RDNA construct in *Epalzeorhynchos frenatus*
GloFish Blue Shark BS2017 RDNA construct in *Epalzeorhynchos frenatus*
GloFish Green Shark GS2017 RDNA construct in *Epalzeorhynchos frenatus*

GloFish Green Betta GBS2019 RDNA construct in *Betta splendens*
GloFish Orange Betta OBS2019 rDNA construct in *Betta splendens*
GloFish Pink Betta PiBS2019 rDNA construct in *Betta splendens*
GloFish Purple Betta PBS2021 rDNA construct in *Betta splendens*

GloFish Orange Catfish OCA2020 rDNA construct in *Corydoras aeneus*
GloFish Pink Catfish PiCA2020 rDNA construct in *Corydoras aeneus*
GloFish Green Catfish GCA2021 rDNA construct in *Corydoras aeneus*

GloFish Orange Pristella OPM2021 rDNA construct in *Pristella maxillaris*
GloFish Green Pristella GPM2021 rDNA construct in *Pristella maxillaris*
GloFish Purple Pristella PPM2021 rDNA construct in *Pristella maxillaris*
GloFish Red Pristella RPM2022 rDNA construct in *Pristella maxillaris*

GloFish Red Angelfish RAF2023 rDNA construct in *Pterophyllum scalare*

IGAs in animals of food-producing species intended for use as models of disease

Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen ATM miniswine ATM-NEO RDNA construct in Yucatan Miniature Swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen LDLR miniswine LDLR-NEO RDNA construct in Yucatan Miniature Swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen SCN5A miniswine SCN5A-NEO RDNA construct in Yucatan Miniature Swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen NF1 miniswine NF1 RDNA construct in Yucatan Miniature Swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen PKD1 miniswine PKD1 +/R3278C-BLAST RDNA construct at exon 29 in Yucatan miniature swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen CLN3 miniswine CLN3 RDNA construct disrupting exon 7 and 8 of CLN3 gene in Yucatan miniature swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen MYH7 miniswine MYH7 RDNA construct in Yucatan Miniature Swine
Exemplar Genetics, LLC (dba Precigen Exemplar), ExeGen CLN2 miniswine CLN2 RDNA construct in Yucatan Miniature Swine

Recombinetics, OssaPig-FH-PCSK9 Miniature Swine PCSK9-D374Y RDNA construct in Ossabaw Miniature Swine
Recombinetics, OssaPig-NF-NF1(FS41) Miniature Swine (Sus scrofa (g.(NC_010454.4)43530892C>T + 43530890_43530889insAGCTT in Ossabaw Miniature Swine)
Recombinetics, YorkaPig-HF-RBM20 (Sus scrofa g.(NC_010456.5)121244982C>A + 121244988-121244989CG>TC + 121244991-121244992AG>TC in Yorkshire Breed Large White Swine)
Recombinetics, OssaPig-LD-NASH Miniature Swine (Sus scrofa g.(NC_010447.5) 5087853-5087855GAC>CTG + 5087858G>C + 5087861T>C + 5087864C>G + 5087871-5087873CTC>GAA in Ossabaw Miniature Swine)
Recombinetics, OssaPig-NF-NF1(NS) Miniature Swine (g.(NC_010454.4)43530860G>T + 43530872C>T + 43530892C>T + 43530899T>C) in Ossabaw Miniature Swine

Sus Clinicals, Oncopig Cancer Model, Cre-inducible Neo-KRASG12D-TP53R167H rDNA construct in the ITPRID1 gene in cross-bred swine

IGAs in Animals Intended for Food Use

Acceligen Inc (a Recombinetics Company), PRLR-SLICK cattle, SLICK alteration disrupting Bos taurus g.(NC_037347.1) fs(39099129-39099368) in exon 9 of PRLR gene in *Bos taurus* (Risk Assessment Summary)

https://www.fda.gov/animal-veterinary/intentional-genomic-alterations-igas-animals/intentional-genomic-alterations-igas-animals-risk-reviewed-igas

Category 3: Approval process

Is the IGA present? What are the hazards associated with introduction of the IGA in the animals? Are there any unintended alterations that might impact safety?

What is the impact of the alteration on animal health/safety? Is the intended phenotype expressed?

Are the genotype and phenotype consistent over the lifespan of the product? Is there a plan for monitoring durability? Is there a contingency/disaster recovery plan, if needed? Is there a post-approval reporting plan?

What are the risks (if any) of direct/indirect effects associated with consumption of edible products derived from the animals with the IGA?

What is the impact on the environment of CVM approving the IGA in the animals (NEPA)?

Does the IGA do what it is intended to do?

Is the labeling truthful and not misleading?

*Described further in Guidance for Industry (GFI) #187A

FDA/CVM Approvals

Name	Traits	Purpose	Approval Date
AquAdvantage Atlantic Salmon	IGA results in Atlantic salmon that reach market size more quickly than non-IGA farm-raised Atlantic salmon	Food	**2015**
SBC LAL-C Chicken	IGA produces a recombinant form of human lysosomal acid lipase protein in egg whites for treatment of patients with lysosomal lipase deficiency	Biopharm	**2015**
LFB R69 Rabbit	IGA produces human recombinant Factor VII zymogen in rabbit milk for the treatment of patients with hemophilia A or B disorders	Biopharm	**2018**
GalSafe™ Pig	IGA results in non-detectable levels of alpha-gal sugar on cell surfaces to be used for food and as a source of human therapeutics	Food/ Biopharm	**2020**

Other considerations

- USDA requirements
  - Labeling
    - Food Safety and Inspection Service labeling regulation
    - "Bioengineered" labeling – USDA Agricultural Marketing Service
  - Slaughter

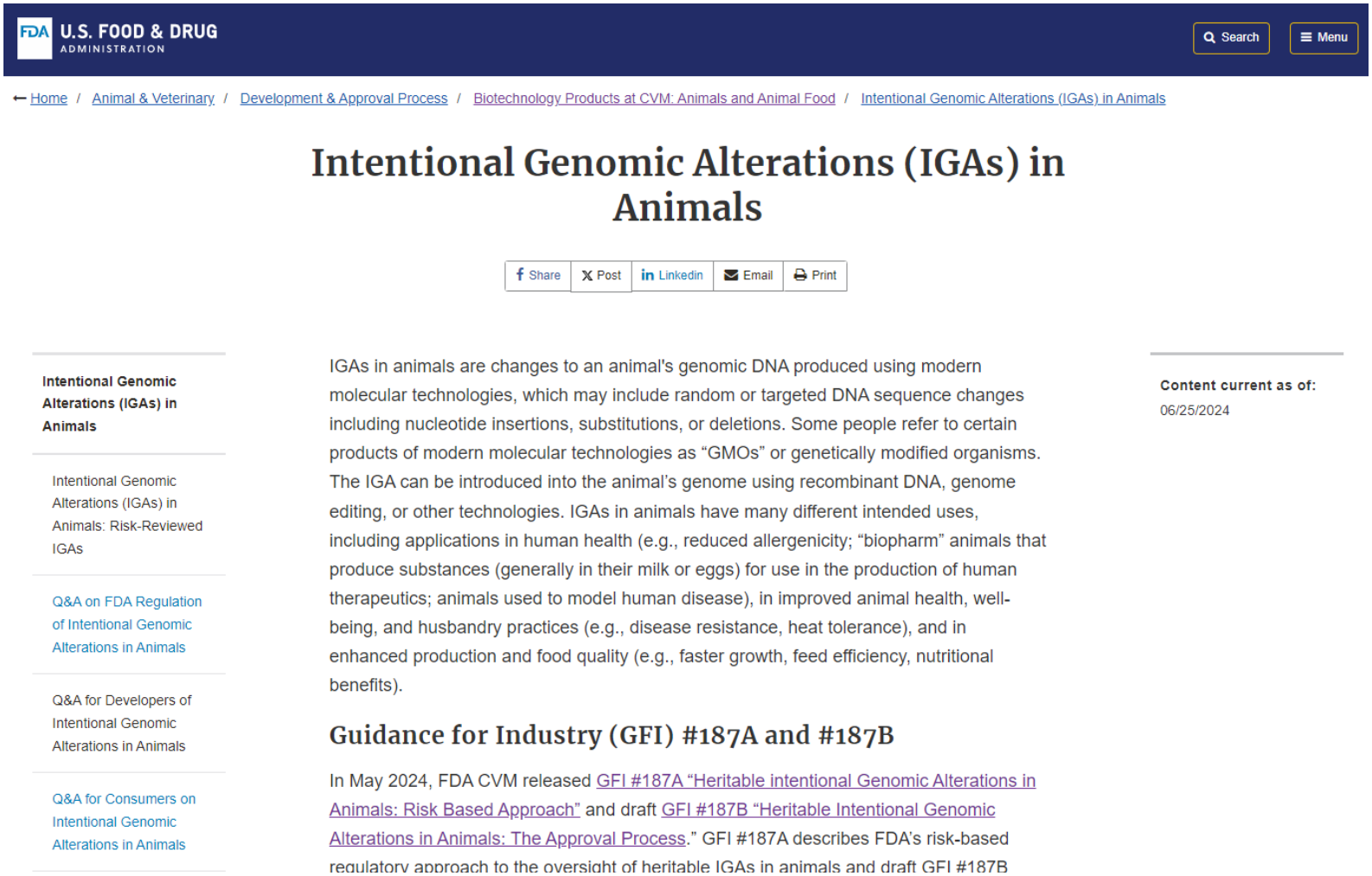
- Breeding
  - Farmers/growers do not need to notify FDA to breed animals with risk-reviewed or approved IGAs

https://www.southernliving.com/culture/pets/pig-names

FDA's Support of IGA Development

- Launched Veterinary Innovation Program (VIP) for animal biotechnology products that provide a benefit to animal or human health, food production, or animal well-being
  - Benefits include VIP Toolkit, pre-review feedback, stopping the review clock, and more
- Animal and Veterinary Innovation Agenda (AVIA) includes expansion of VIP to include VIP Plus
  - Research work, including collaboration with National Institute of Standards and Technologies
  - Access to advanced computational tools such as precisionFDA

Helpful resources



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Intentional Genomic Alterations (IGAs) in Animals

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Intentional Genomic Alterations (IGAs) in Animals

Intentional Genomic Alterations (IGAs) in Animals: Risk-Reviewed IGAs

Q&A on FDA Regulation of Intentional Genomic Alterations in Animals

Q&A for Developers of Intentional Genomic Alterations in Animals

Q&A for Consumers on Intentional Genomic Alterations in Animals

IGAs in animals are changes to an animal's genomic DNA produced using modern molecular technologies, which may include random or targeted DNA sequence changes including nucleotide insertions, substitutions, or deletions. Some people refer to certain products of modern molecular technologies as "GMOs" or genetically modified organisms. The IGA can be introduced into the animal's genome using recombinant DNA, genome editing, or other technologies. IGAs in animals have many different intended uses, including applications in human health (e.g., reduced allergenicity; "biopharm" animals that produce substances (generally in their milk or eggs) for use in the production of human therapeutics; animals used to model human disease), in improved animal health, well-being, and husbandry practices (e.g., disease resistance, heat tolerance), and in enhanced production and food quality (e.g., faster growth, feed efficiency, nutritional benefits).

Guidance for Industry (GFI) #187A and #187B

In May 2024, FDA CVM released GFI #187A "Heritable intentional Genomic Alterations in Animals: Risk Based Approach" and draft GFI #187B "Heritable Intentional Genomic Alterations in Animals: The Approval Process." GFI #187A describes FDA's risk-based regulatory approach to the oversight of heritable IGAs in animals and draft GFI #187B

Content current as of:
06/25/2024

Helpful resources

Helpful resources

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Intentional Genomic Alterations (IGAs) in Animals

Cell and Tissue Products for Animals

Center for Veterinary Medicine (CVM) Animal Biotechnology Products Resource Center

Español

for Certain Applications for Intentional Genomic Alterations in Animals and Animal Cells, Tissues, and Cell- or Tissue-Based Products

On September 15, 2023, the FDA announced expanded features of the Veterinary Innovation Program as part of the agency's Animal and Veterinary Innovation Agenda. VIP Plus includes new tools that will assist product development and continually improve the efficiency of the FDA's review process of VIP products. For more information please see VIP Plus.

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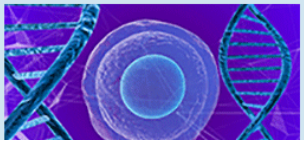

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