Progress of Metabolomics-Centric Multi-Omics Research in Medicine.

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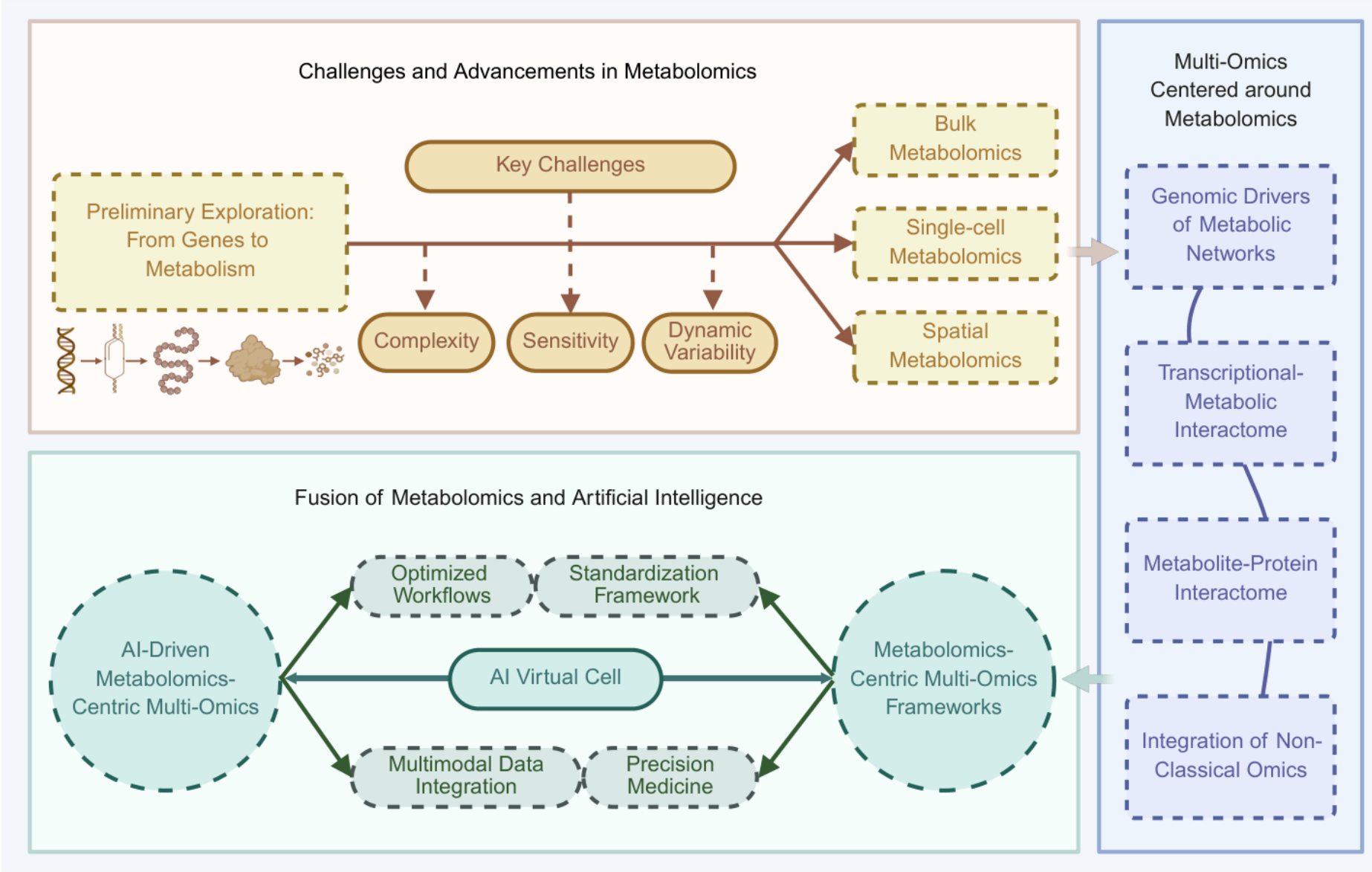
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Introduction & Highlights

- Proposes a metabolomics-centric paradigm as the functional anchor for interpreting genotype-phenotype relationships.
- Surveys the technological evolution from bulk to single-cell and spatial metabolomics.
- Examines AI-driven multimodal data integration to overcome computational challenges.
- Identifies the AI Virtual Cell (AIVC) as a pivotal future direction for predictive precision medicine.



The Evolution of Metabolomic Technologies

Metabolomics Technologies (Table 2 Summary)

- **Bulk:** Broad coverage (1000+), high throughput. *Best for: Biomarker discovery.*
- **Single-cell:** Resolves intercellular heterogeneity (50-200 metabolites). *Best for: Rare cell subpopulations.*
- **Spatial:** Micron-scale resolution (MALDI/DESI-MSI), preserves tissue context. *Best for: Tumor heterogeneity mapping.*

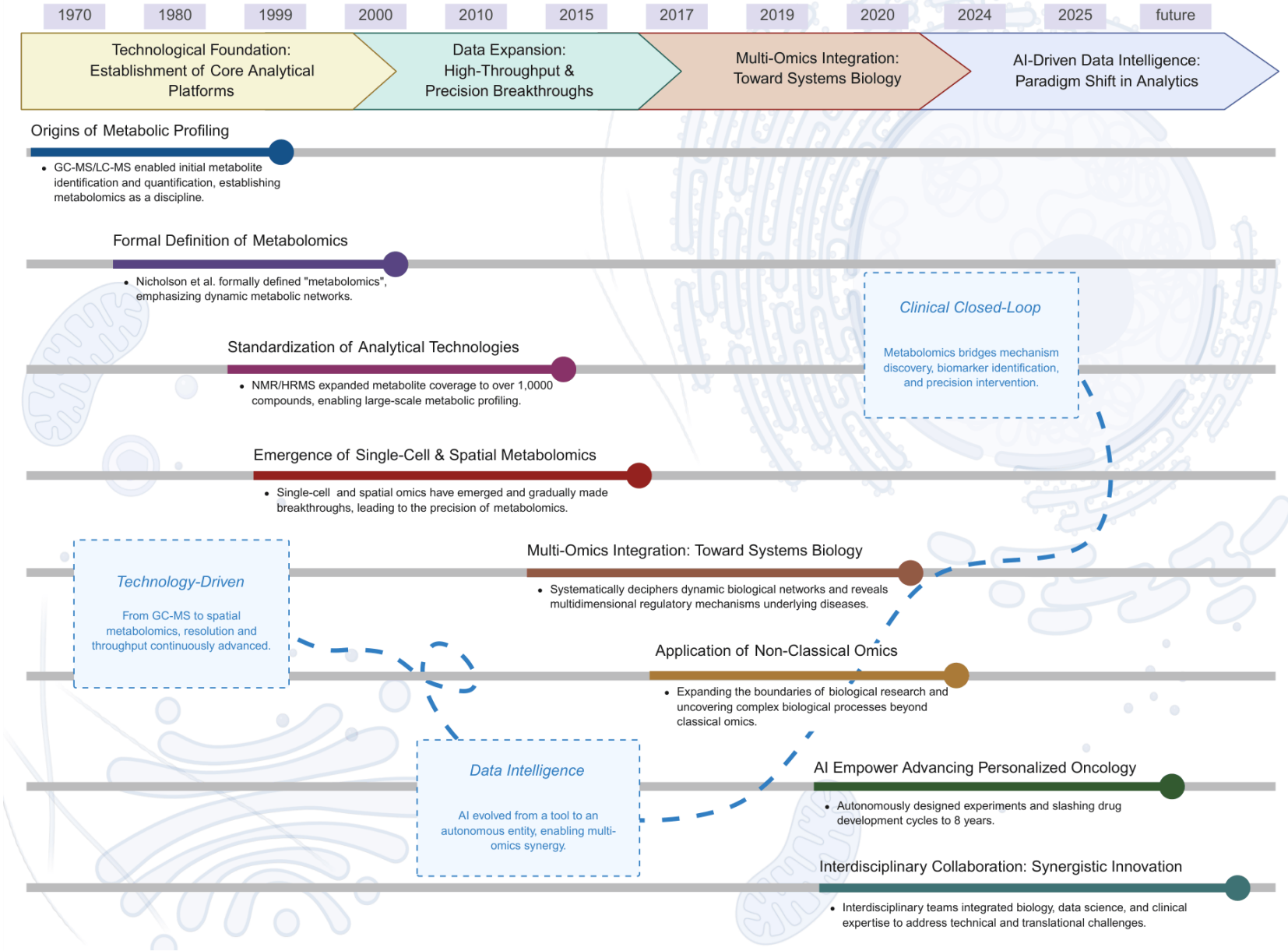


Figure 1 The evolution of metabolomics: paradigm shift toward multi-omics integration.

A Metabolomics-Centric Multi-Omics Framework

Omics Emphasis Comparison (Table 1 Summary)

Genomics (WGS)	Reveals genetic basis & stable variations.
Transcriptomics (RNA-seq)	Captures gene expression dynamics.
Proteomics (MS)	Detects direct functional linkages & modifications.
⭐Metabolomics (LC/GC-MS, NMR)	Provides direct phenotypic reflection and high sensitivity to dynamic physiological changes.

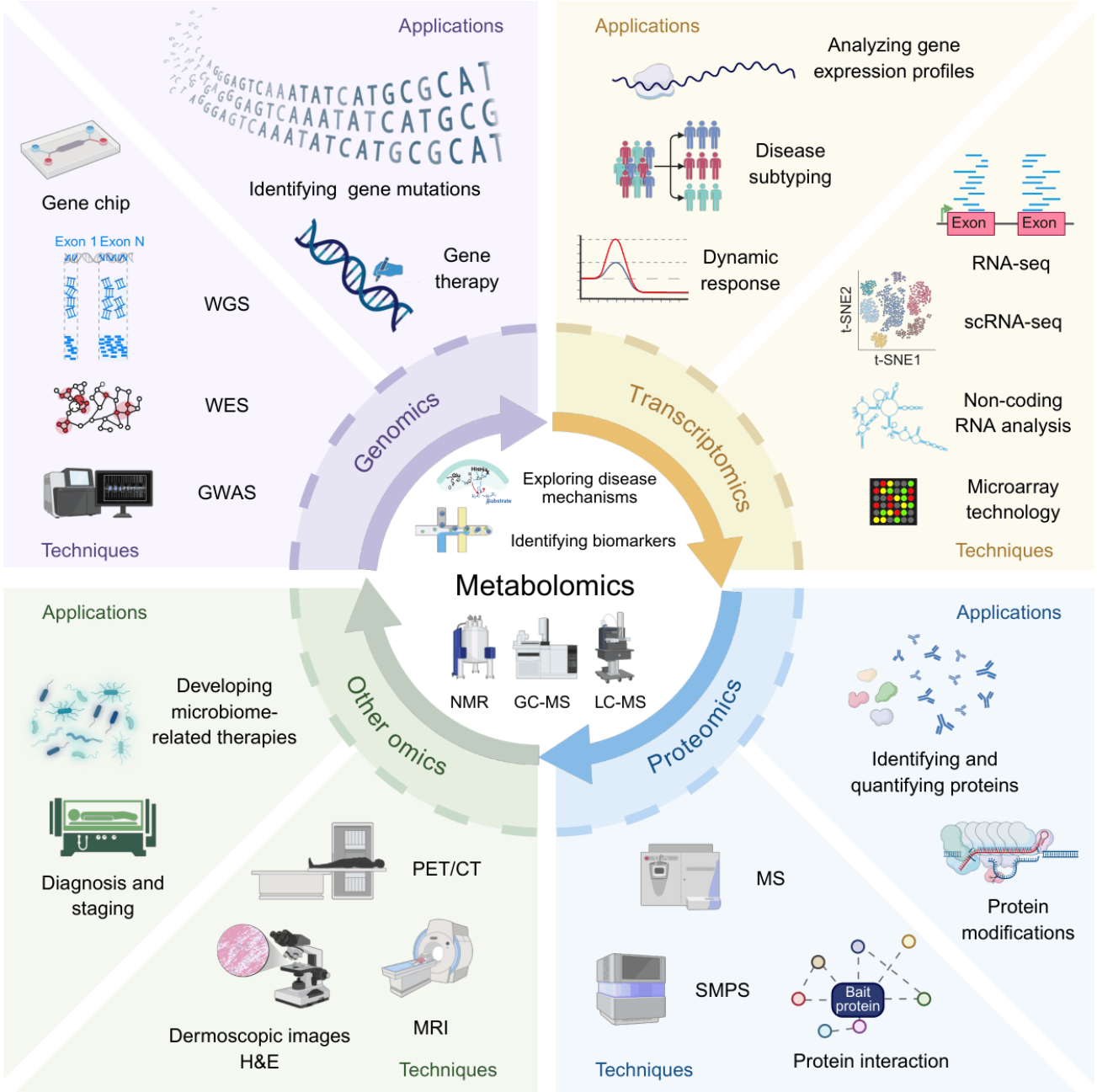


Figure 2 Multi-omics integration in disease research.

AI-Driven Metabolomics-Centric Multi-Omics Integration

Multi-Omics Integration Methodologies

(Table 3 Summary)

- **Network-Based** (e.g., SNF, CIMLR): Fuses sample similarity networks; robust to noise.
- **Statistics & Matrix Factorization** (e.g., mixOmics, MOFA): Unified statistical framework for linear relationships.
- **DL-Based** (e.g., MOGONET, Subtype-GAN): Advanced neural architectures for modeling complex, non-linear cross-omics relationships.
- **User-Friendly Platforms** (e.g., BiomiX): Workflow-driven interfaces for exploratory analysis.

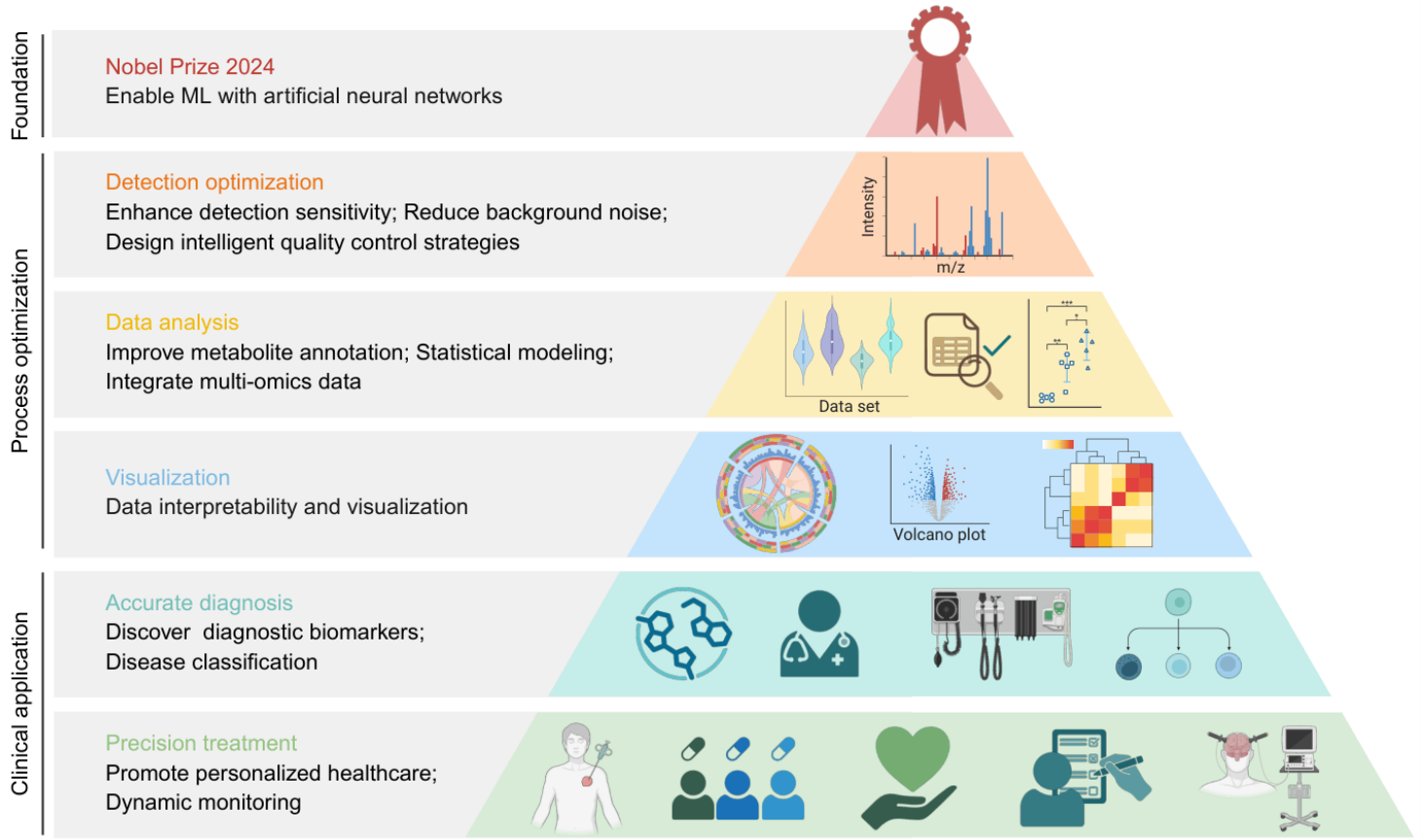


Figure 3 AI-driven metabolomics: from neural network foundations to precision medicine implementation.

Key Milestones in AI and Omics Applications

Translational Discoveries in Precision Medicine

(Table 4 Summary)

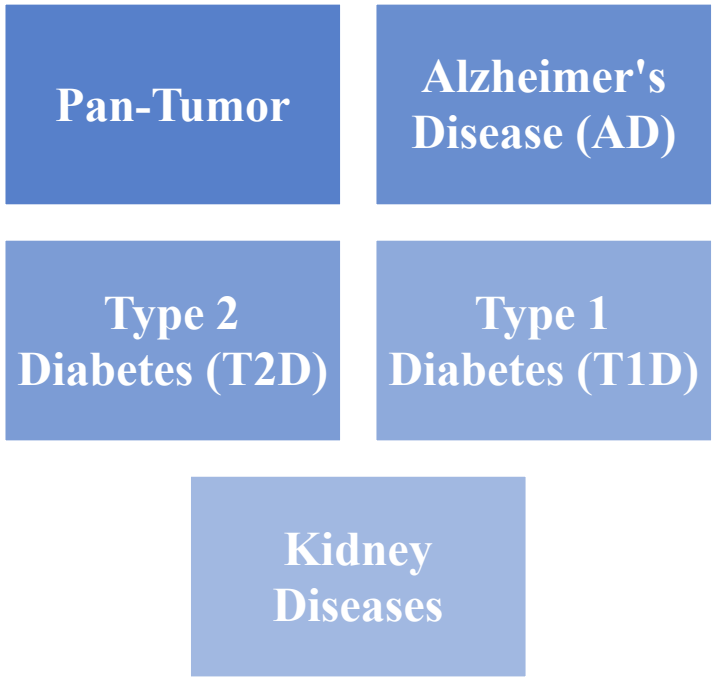
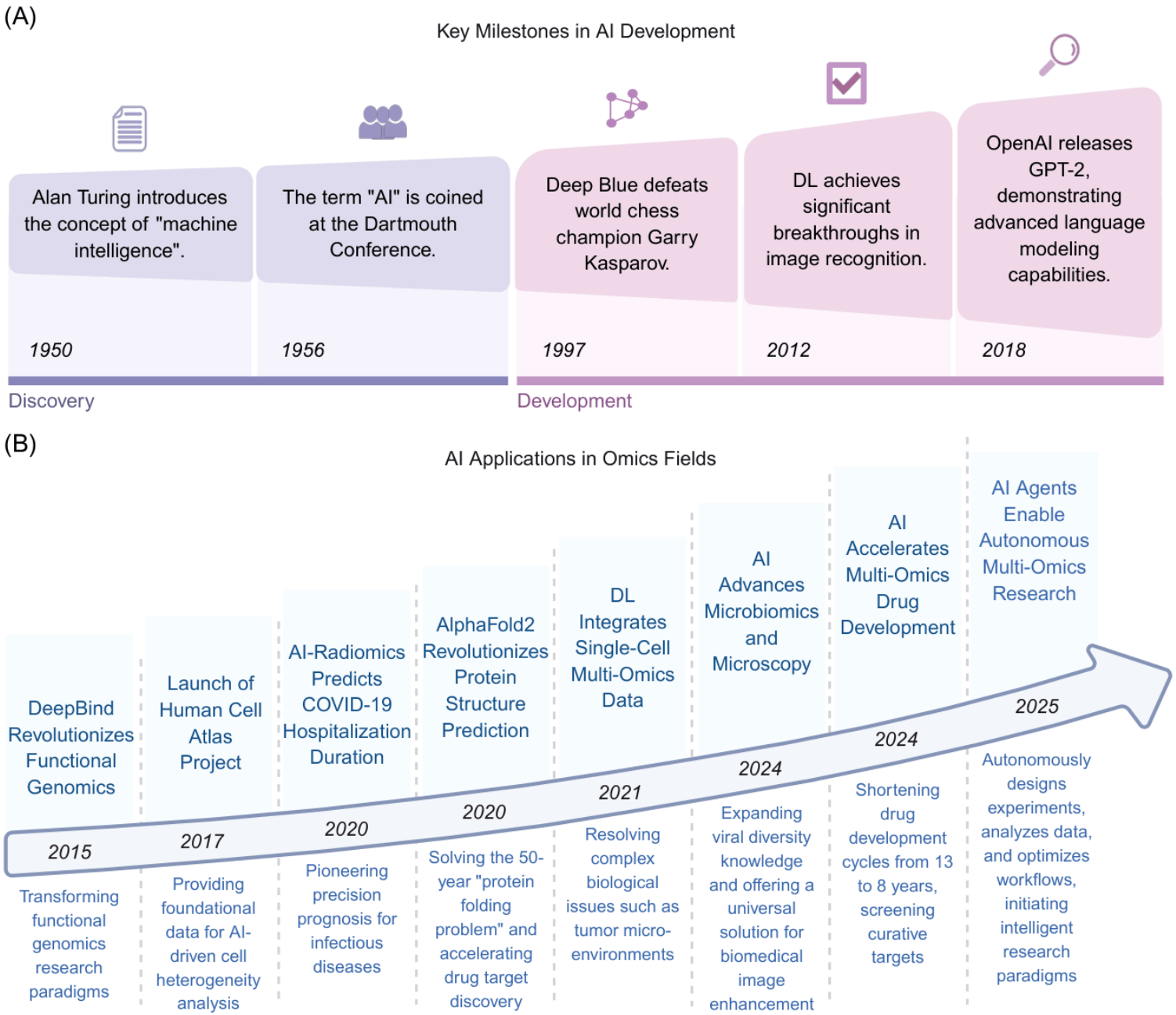


Figure 4 Key milestones in AI development and its application areas in omics fields.



Conclusion & Future Perspectives

Future Direction: The AI Virtual Cell (AIVC)

Key Takeaways

- Digital Twin: AIVC functions as a digital twin of a real biological cell.
- Metabolomics as Anchor: Provides the closest readout of phenotype to constrain model predictions.
- Goal: Enable predictive modeling, personalized therapeutic design, and clinical deployment.

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