EDITION 1 · 2026

Network Medicine — A Reading List

A curated path through systems thinking in clinical practice. Ordered for accessibility, not chronology.

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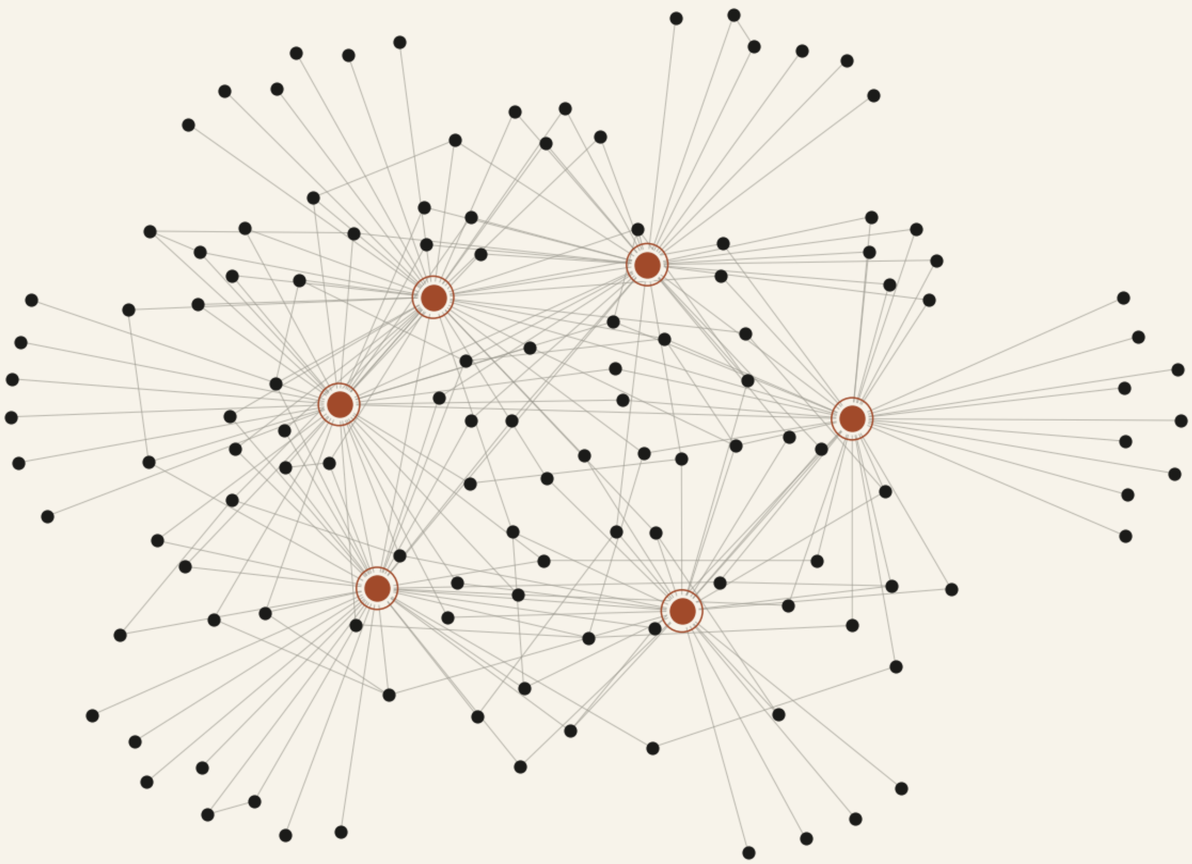
castoremethod.com



A fragment of the interactome.

Hubs in rust. Ordinary nodes in ink. Edges between them.
This is what you'll learn to see.

Contents

What follows, in order.

Each tier is designed to be read in sequence. Skipping ahead is allowed but rarely useful — the foundations carry the weight.

How to Use This Reading List

A short Feynman-style note before you begin.

If you can't explain network medicine to a curious friend in three sentences, you don't yet understand it. So before you open a single paper on the list that follows, read this front-matter twice. The goal is for you to be able to teach this — not just consume it.

Here is the whole field in one breath: a disease is rarely the failure of one gene. It is the failure of a connected pattern of genes, proteins, and metabolites — a network. Treat the pattern, not the part. That's it. Everything in this reading list is a deeper way of seeing that single sentence.

The list is organized in four tiers. Read top to bottom. Each tier builds on the last. Tier 1 is the on-ramp; Tier 4 is the wider context that makes the whole project make sense for clinicians and clients.

The annotations are the lesson. The books are the practice. Read the annotation first. If the annotation is enough for what you need today, that's a complete unit of learning — move on. If you want the mechanism in your hands, pick up the source.

> **HOW TO READ THIS GUIDE**
> Read top to bottom. One entry per week. Redraw one diagram from memory. Pair each paper with a real case.

If after Tier 1 you find yourself muttering 'so it's just systems thinking applied to molecules' — yes. That's the point. The list is here so you can teach it that simply, with receipts.

Chapter 1

Why Network Medicine

The case for treating the pattern, not the part.

THE 80/20 — WHAT YOU ACTUALLY NEED TO REMEMBER

- Most chronic diseases are network failures, not single-gene failures.
- The interactome is the wiring diagram of the cell — proteins, genes, metabolites, all linked.
- Disease genes cluster in modules. The same module can touch several diseases at once.
- Hubs are nodes with many connections. Knock one out and the network staggers.
- Edgetics: many mutations break connections, not the protein itself.
- Effective therapy often means hitting several nodes lightly, not one node hard.

The core problem

Modern medicine inherited a beautiful idea from the 20th century: one gene, one protein, one drug, one disease. It worked spectacularly for a handful of monogenic conditions — sickle cell, cystic fibrosis, certain leukemias. For everything else, the idea has been bending under its own weight for thirty years.

Think of a clock. A clock has dozens of parts, but they only matter because they're connected. Now imagine your only tool is a hammer, and your only theory is that broken clocks have one bad part. You will spend a lifetime smashing gears.

A single-target drug for a multi-node disease is a hammer for a clock. It might dent something. It will not fix time.

Hub and spoke

Picture an airline route map. Take out a small regional airport and almost no one notices. Take out Atlanta and the country grinds. Cells are built the same way. A handful of hub proteins coordinate dozens of pathways. Most diseases are not the failure of a single random node — they are the destabilization of a hub or the cluster of nodes around it. Network failure, not node failure.

The picture

Below is a stylized fragment of an interactome — proteins as nodes, interactions as edges. Three high-degree hubs are highlighted. Notice how many ordinary nodes depend on them. Notice how losing a single hub fractures the local neighborhood.

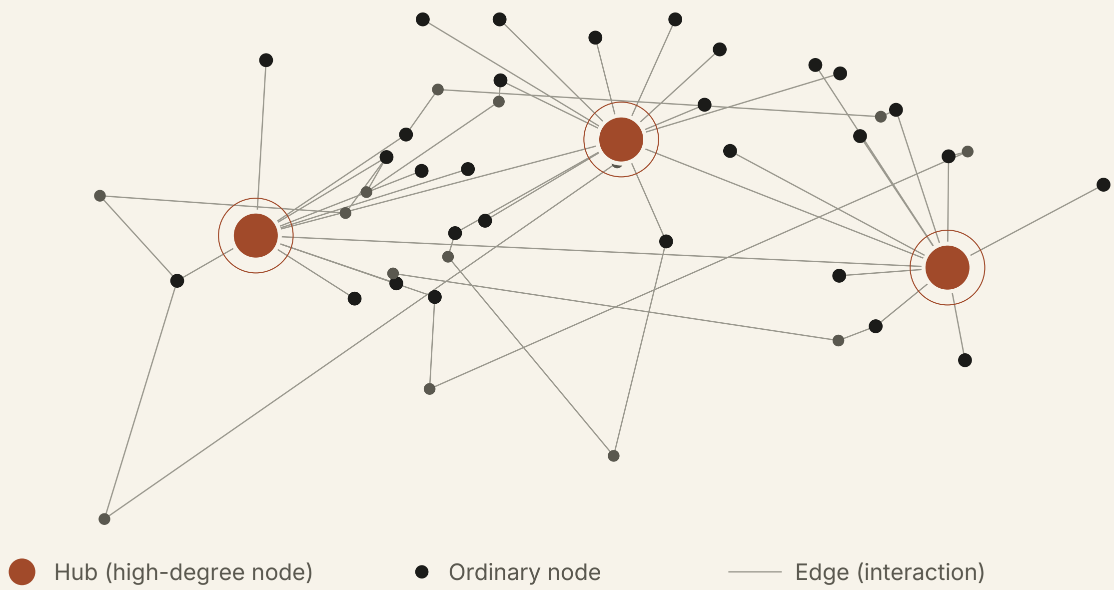


Figure 1. A simplified interactome. Hubs (rust) carry disproportionate load. Knock out a hub, the whole system staggers.

> **MNEMONIC**
> Treat the network, not the node.

This is the whole reason the rest of the reading list exists. Everything you read from here on out is the field learning to see, measure, and intervene at the level of the network rather than the level of the part. The tools change. The conviction does not.

Chapter 2

The Five Ideas You Need Before You Read Anything

Five letters. Memorize them. Everything else is commentary.

> ACRONYM
> N.O.D.E.S. — Network · Omics · Disease modules · Edgetics · Systems pharmacology.

N — Network topology

Networks have shape. A few nodes have very many connections (hubs); most have very few. The number of connections a node has is its degree. Groups of densely interconnected nodes form modules. Real biological networks are scale-free: the degree distribution follows a power law, which is why removing a random node almost never matters but removing the right hub can be catastrophic. Example: p53 sits at the center of cell-cycle and apoptosis circuitry — its loss reverberates through dozens of pathways at once.

O — Omics integration

One layer is never enough. The genome tells you what can happen; the transcriptome what is being read; the proteome what is being built; the metabolome what is actually happening. Network medicine layers these maps on top of each other so a perturbation in DNA can be traced to a downstream protein and the metabolite shift that finally lands in the clinic. Example: in coronary artery disease, GWAS hits alone explain little — but mapped onto protein and metabolic networks, they cluster meaningfully around lipid handling and inflammation.

D — Disease modules

Genes associated with a disease are rarely scattered at random. They co-localize in a neighborhood of the interactome — a disease module. Modules for related diseases overlap. The closer the modules in network space, the more likely the diseases share symptoms, comorbidities, and (sometimes) drugs. Example: the modules for asthma and inflammatory bowel disease sit close enough on the interactome to predict (correctly) that anti-inflammatory biologics designed for one would have signal in the other.

E — Edgetics

A mutation can destroy a protein, but more often it does something subtler — it changes which other proteins that protein can talk to. The node still exists; the edges change. This is edgetics. It explains why two patients with mutations in the 'same' gene can present with completely different diseases: they have lost different connections. Example: certain p53 mutants retain function but lose the ability to bind specific co-factors, producing tumor profiles distinct from p53 knockouts.

S — Systems pharmacology

If diseases are network failures, drug development changes shape. We stop pretending the best drugs are exquisitely selective. We design — on purpose — molecules that touch several nodes lightly, restoring the pattern. Some of the most effective drugs in cardiology (statins, metformin, aspirin) were always polypharmacological; we just couldn't see it. Example: metformin acts on AMPK, mitochondrial complex I, and gut microbiome composition at once — and its mortality benefit may come from the combination, not any one mechanism.

If you can recite N.O.D.E.S. from memory and give an example of each, you have the scaffold. Now you can hang the reading list on it.

Bridge

How the Four Tiers Fit Together

Why the order matters more than any single entry.

There are four tiers. They are not difficulty levels and they are not chronological. They are functional — each tier does a particular job for the reader. Skip any one of them and the whole list becomes a list of books rather than an education.

Tier 1 — Vocabulary and intuition.

Tier 1 is where you learn the words and the pictures. Hubs. Modules. Scale-free. Interactome. Once these become first-language for you, every other paper in this list becomes 2-3x easier to read. Skip Tier 1 and Tier 2 will feel like reading a foreign technical manual.

Tier 2 — The mechanisms underneath the vocabulary.

Tier 2 is where the field stops being a metaphor. You'll see how interactomes are actually built (and where they're wrong); how disease modules are defined statistically; how network distance predicts comorbidity in real claims data. This is the discipline-establishing layer.

Tier 3 — What changes in practice.

Tier 3 is where it touches the clinic and the drug pipeline. Polypharmacology by design. Drug repurposing through network proximity. Gene regulatory networks as the wiring under your prescription pad. This is the tier that should change what you do on Monday.

Tier 4 — The wider biology no network paper will teach you.

Tier 4 is the ecology around the network: chronic stress, allostatic load, mitochondrial function, the gut microbiome. The hard-core network medicine literature mostly assumes these are 'inputs.' For a clinician or coach, they are the daily clinical reality. Tier 4 is what makes the model usable in human beings, not just spreadsheets.

> THE POINT
>
> Tier 1 lets you talk. Tier 2 lets you reason. Tier 3 lets you act.
> Tier 4 lets you treat humans.

The Reading List

Four tiers. Read top to bottom.

Each entry below shows the title, authors, year, format, and an Anthony-voiced note that tells you why it matters and what to take from it. Every title is a clickable link to the source.

The map you'll be drawing

Before the entries, one more picture. The whole project of this list is to teach you to see figures like the one below — two disease modules sitting in the same neighborhood of the interactome, sharing nodes. That overlap is what predicts comorbidity. That overlap is what predicts whether a drug for one will work on the other. By Tier 2 you'll be drawing diagrams like this from memory.

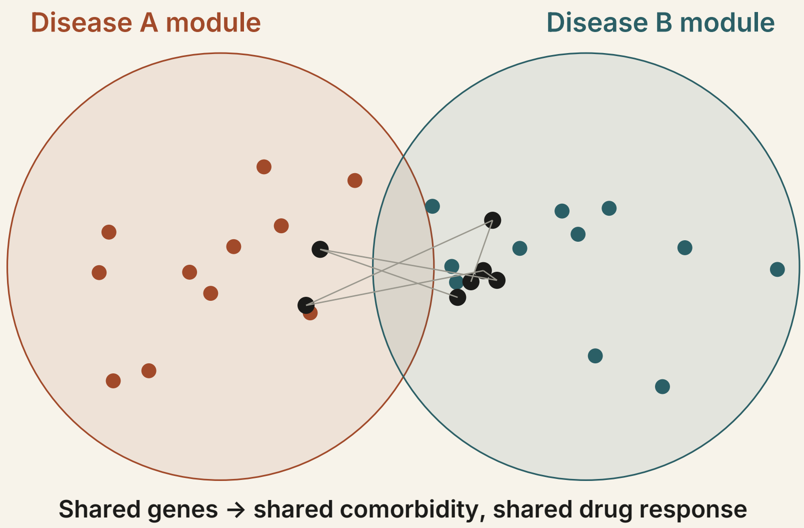


Figure 2. Two disease modules in the interactome. The shared nodes (ink) are where comorbidity, shared symptoms, and drug-repurposing opportunities live.

Tier 1

Start Here

Gentle on-ramps. The vocabulary, the metaphors, the why.

Network Medicine — From Obesity to the Diseasome

Albert-László Barabási · 2007 · Paper · NEJM editorial

Read this if you're trying to understand why the field exists at all — written for clinicians, not network scientists. The single most useful chunk is the three-layer figure (molecular network → disease network → social network). If you remember nothing else from Tier 1, remember that diagram.

Uncovering Disease-Disease Relationships Through the Incomplete Interactome

Menche, Sharma, Kitsak, Ghiassian, Vidal, Loscalzo, Barabási · 2015 · Paper · Science

Read this if you're trying to understand how 'disease modules' are actually measured, and why distance in the interactome predicts symptom overlap and comorbidity. The single most useful chunk is the disease-distance result: when two disease modules overlap in network space, the diseases co-occur in patients. This single insight reframes comorbidity from coincidence to topology.

Linked: The New Science of Networks

Albert-László Barabási · 2002 · Book · trade paperback

Read this if you're trying to understand the intuition for scale-free networks before any math. Read it like a novel. The single most useful chunk is chapters on hubs and preferential attachment. Once you see why 'the rich get richer' shows up in protein interactions, the rest of network biology stops feeling mysterious.

An Introduction to Systems Biology

Uri Alon · 2006 / 2019 2nd ed. · Textbook

Read this if you're trying to understand design principles of biological circuits — feedback, feed-forward loops, robustness — at a level a clinician can actually follow. The single most useful chunk is the chapter on network motifs. Once you've seen the same handful of motifs across yeast, E. coli, and human cells, you stop being surprised by anything in the rest of the list.

Tier 2

Mechanisms

The papers that made this a discipline rather than a metaphor.

Network Medicine: A Network-Based Approach to Human Disease

Barabási, Gulbahce, Loscalzo · 2011 · Paper · Nature Reviews Genetics

Read this if you're trying to understand the canonical statement of the field — what it is, what it isn't, what tools it brings. The single most useful chunk is the discussion of local hypothesis vs. global hypothesis: disease genes cluster locally in the interactome, but their effects propagate globally. Carry that distinction into every conversation.

Interactome Networks and Human Disease

Vidal, Cusick, Barabási · 2011 · Paper · Cell

Read this if you're trying to understand how interactomes are built — yeast two-hybrid, affinity purification, the limits of each. Without this you'll over-trust whatever PPI database you happen to download. The single most useful chunk is the section on coverage and incompleteness. Every interactome map is a sketch — knowing where the gaps are is half the skill.

Network Medicine: Complex Systems in Human Disease and Therapeutics

Joseph Loscalzo, Albert-László Barabási, Edwin Silverman (eds.) · 2017 · Book · Harvard University Press

Read this if you're trying to understand the definitive textbook. Use it as a reference, not cover-to-cover. The single most useful chunk is the chapters on cardiovascular disease and pulmonary disease — they show what network medicine looks like in actual clinical specialties.

The Human Disease Network

Goh, Cusick, Valle, Childs, Vidal, Barabási · 2007 · Paper · PNAS

Read this if you're trying to understand the foundational diseasome paper: a bipartite graph of diseases linked by shared genes. The figure alone is worth the read. The single most useful chunk is the observation that essential genes tend to be hubs while disease genes tend to be peripheral — and what the exceptions (cancer) tell you about somatic vs. germline disease.

Network-Based Prediction and Population-Based Validation of In Silico Drug Repurposing

Cheng, Desai, Tang, Erez, Maron, Loscalzo et al. · 2018 · Paper · Nature Communications

Read this if you're trying to understand what 'network proximity' between a drug's targets and a disease module actually predicts in real-world patient data. The single most useful chunk is the validation step — pulling 220 million patient-years of insurance claims to confirm that drugs near a disease module in network space actually reduce incidence of that disease. This is the field cashing the check.

Tier 3

Practice

How network thinking changes drug discovery and clinical reasoning.

Network Pharmacology: The Next Paradigm in Drug Discovery

Andrew L. Hopkins · 2008 · Paper · Nature Chemical Biology

Read this if you're trying to understand why pharma's holy grail — the perfectly selective drug — was the wrong target all along, and what to chase instead. The single most useful chunk is the polypharmacology argument: most successful drugs hit several targets. The future is to design that multiplicity deliberately rather than discover it after approval.

Structure and Dynamics of Molecular Networks: A Novel Paradigm of Drug Discovery

Csermely, Korcsmáros, Kiss, London, Nussinov · 2013 · Review · Pharmacology & Therapeutics

Read this if you're trying to understand the dynamic side — networks aren't static wiring, they re-wire under stress and over time. This is where allostasis and pharmacology meet. The single most useful chunk is the discussion of edgetic drugs and allosteric pharmacology: rather than blocking a protein, modulate its interactions. This is the conceptual bridge to systems pharmacology in chronic disease.

Constructing Gene Regulatory Networks Using Epigenetic Data (SPIDER / PANDA family)

Sonawane, Weiss, Glass, Sood et al. · 2021 · Paper · npj Systems Biology and Applications

Read this if you're trying to understand how gene regulatory networks are actually inferred from messy real data, and why epigenetics matters for the wiring. The single most useful chunk is the comparison between motif-only and epigenetics-informed networks. It's a lesson in why method choice changes what you 'see' in the network.

Network Medicine in Cardiovascular Research

Leopold, Loscalzo et al. · 2020 · Review · Cardiovascular Research

Read this if you're trying to understand what network medicine looks like in the one organ system where it's most mature. The single most useful chunk is the case studies on heart failure and pulmonary hypertension — how disease modules redrew the boundaries between conditions previously treated as separate.

Tier 4

Adjacent But Essential

Network medicine is incomplete without the body's regulatory ecology — stress, mitochondria, metabolism.

Why Zebras Don't Get Ulcers

Robert M. Sapolsky · 2004 (3rd ed.) · Book

Read this if you're trying to understand the only book on this list that doesn't say 'network' once, and yet is exactly about network failure under chronic load. The single most useful chunk is the chapters on the HPA axis and allostatic load. If you only ever explain stress physiology to clients in one framework, use this one.

Stress, Adaptation, and Disease: Allostasis and Allostatic Load

Bruce S. McEwen · 1998 · Paper · NYAS / NEJM-era review

Read this if you're trying to understand the formal definition of allostatic load — the cumulative cost of repeatedly recalibrating your physiology. The single most useful chunk is the four pathways to allostatic load (frequent stressors, failure to habituate, failure to shut off, inadequate response). These are the failure modes of a regulatory network. Memorize them.

A Mitochondrial Paradigm of Metabolic and Degenerative Diseases, Aging, and Cancer

Douglas C. Wallace · 2005 · Paper · Annual Review of Genetics

Read this if you're trying to understand why mitochondria are not just organelles but a parallel regulatory network — energetic, hormonal, signaling — and what happens when that network degrades. The single most useful chunk is the model of energetic threshold: cells tolerate accumulating mitochondrial damage until they cross a tissue-specific threshold, then fail abruptly. Network failure as a step function.

Metabonomics & Integrative Biology

Jeremy K. Nicholson and colleagues · ongoing · Review program · Imperial College

Read this if you're trying to understand the metabolic layer of the network — how a single metabolic fingerprint can integrate genetic, microbial, and environmental input. The single most useful chunk is the gut-microbiome / host-metabolism axis. It's the clearest demonstration that the body's network extends past the cell membrane and across species lines.

Chapter 3

How to Actually Read This List

A practice, not a syllabus.

Read in tiers, not in order of publication.

The temptation, if you came up through any scientific training, is to read chronologically. Resist it. Network medicine reads backwards when you go by date — the editorials and the textbooks make the foundational papers easier, not harder. Tier 1 first. Always.

One entry per week.

That's roughly four months of steady reading for the whole list. There's no prize for finishing faster, and there's a real penalty for skimming — you'll mistake familiarity for understanding. Block one ninety-minute session per week. Same chair, same coffee.

Redraw one diagram from memory.

After each entry, close the paper and try to reproduce one figure from it on a blank sheet. You will fail the first few times. That failure is the point — it shows you which parts of the diagram you understood and which you only recognized. Fix the gap. Move on.

Pair every paper with a case.

For each entry, choose one patient, one client, or one person you know whose story illustrates the paper's central idea. The papers were written about populations; they live in individuals. If you can't think of a case, you don't understand the paper yet.

> **THE RULE**
> Read · Redraw · Recall · Re-case. Then move on.

The Teach-It-Back Checklist

Six questions. If you can answer them out loud, you can teach this.

1. Why do disease modules overlap matter more than individual gene lists?

Because overlap predicts shared symptoms, shared comorbidities, and shared drug responses. A gene list is a parts inventory. Overlap is the wiring diagram.

2. What does a 'shortest-path' distance in the interactome predict?

How closely two diseases are related at the molecular level — and, downstream, whether a drug developed for one will plausibly help the other. Network distance is clinical distance.

3. What is the difference between a node mutation and an edgetic mutation?

A node mutation removes or disables a protein. An edgetic mutation leaves the protein intact but changes its interaction partners. Different patients, same gene, different disease.

4. Why do hubs matter more than ordinary nodes?

Because they coordinate disproportionately many connections. Random failures are absorbed; targeted hub failures cascade. This is why scale-free networks are robust yet fragile.

5. Why isn't a perfectly selective drug always the best drug?

Because the disease is rarely a single-node failure. Hitting one node hard rarely restores the pattern; hitting several nodes lightly often does. Polypharmacology is a feature, not a bug.

6. Where does allostatic load fit in a network model?

It is the accumulated cost of the regulatory network repeatedly re-stabilizing under chronic perturbation. The network doesn't break — it gets expensive to maintain, and then it breaks.

Glossary

Twelve terms. Learn them; the rest of the field falls into place.

NODE
A single component in a network — a gene, protein, metabolite, or sometimes a disease or a patient. The 'thing.'

EDGE
A connection between two nodes. In biology it usually means a physical interaction, a regulatory link, or a correlation. The 'relationship.'

HUB
A node with an unusually high number of edges. In scale-free networks, a few hubs do disproportionate work.

DEGREE
The number of edges a node has. Hubs are high-degree by definition.

MODULE
A densely interconnected cluster of nodes — a neighborhood. Disease modules are the clusters that matter clinically.

INTERACTOME
The full network of physical and functional interactions inside a cell. Incomplete by construction, but improving every year.

PERTURBATION
Any change to a network — a mutation, a drug, a signal — and the cascade it produces. The unit of analysis in systems medicine.

EDGETICS
The study of mutations that change a protein's interactions without abolishing its function. Same node, different edges.

OMICS
The collective suffix for whole-system measurements — genomics, transcriptomics, proteomics, metabolomics. Layered into one map, these become network medicine's input.

ALLOSTATIC LOAD
The accumulated wear-and-tear of repeatedly re-stabilizing physiology under stress. The cost of keeping a network in spec.

POLYPHARMACOLOGY
The design (or accidental discovery) of a drug that acts on several targets at once. The therapeutic native form of network medicine.

NETWORK PROPAGATION
An algorithmic technique that spreads a signal from a starting node along network edges to find related nodes. The mathematical engine behind disease-gene discovery and drug repurposing.

Closing Note

A word before you start.

The body doesn't read the textbook. It reads the network.

Once you learn to see the network, the textbook starts making more sense — but you'll never need it the same way again. The protocols you've memorized will look less like commandments and more like rough heuristics, useful in the average case and quietly wrong in the cases that actually walk into your office.

That shift is uncomfortable. It's also the only honest direction medicine has left to go. Reductionism gave us antibiotics and insulin and statins, and we should be grateful for every one of them. It will not give us a cure for the chronic, multi-system, allostatically loaded conditions that fill modern clinics. Network thinking might.

Read the list. Redraw the diagrams. Carry a few patients in your head while you do it. By the end, you won't just understand network medicine — you'll find it hard to think any other way.

— Anthony Castore
SSRP Fellow · The CASTORE Method

About

The Author & The Method

Why this list exists, and what it's for.

Anthony Castore

Anthony Castore is an SSRP Fellow and the founder of the CASTORE Method — a clinical practice and research program focused on adaptive capacity: the body's ability to absorb load, restore baseline, and learn from perturbation. His work pairs the language of network medicine with the daily realities of human coaching: sleep, training, nutrition, stress, hormones, and recovery.

This reading list is the front matter of that practice. It exists because every client who walks through the door has already been told that their condition is the failure of one part. Most of the time, it isn't. The list is the receipts.

The CASTORE Method

Capacity · Adaptation · Stress signal · Timing · Output · Recovery · Energy. The method is a network model of human performance and resilience. It treats the body the way this reading list treats biology — as a connected system whose patterns matter more than its parts.

How to share this guide

This guide is free to share with attribution. If a friend, colleague, or client would benefit, send them the PDF directly or point them to castoremethod.com. The goal is more clinicians and more clients thinking in networks. Everything else is downstream of that.

Edition 1 · 2026 · Built to Adapt · castoremethod.com

Appendix

Index of Authors

The people whose work this list rests on.

Uri Alon — Weizmann Institute. Systems biologist who turned 'network motifs' into a teachable, universal vocabulary. His textbook is the single best on-ramp for anyone serious about circuits in biology.

Albert-László Barabási — Northeastern University. The physicist who brought scale-free networks into biology. If one author is the through-line of this list, it is him.

Feixiong Cheng — Cleveland Clinic. Pioneered network proximity as a quantitative predictor of drug-repurposing success and validated it in massive real-world claims data.

Peter Csermely — Semmelweis University. Reframed pharmacology around dynamic networks and allosteric modulation; bridge between systems biology and chronic disease.

Andrew L. Hopkins — Exscientia, formerly Pfizer/Dundee. Wrote the founding argument for network pharmacology: stop chasing perfect selectivity, start designing intelligent multiplicity.

Joseph Loscalzo — Brigham and Women's / Harvard Medical School. Clinician-scientist who made network medicine a serious cardiology research program and co-edited the field's definitive textbook.

Bruce S. McEwen — Rockefeller University (1938–2020). Defined allostatic load. The vocabulary of chronic stress in modern medicine is largely his.

Jorg Menche — University of Vienna. Lead author of the disease-distance paper; quantified what it actually means for two diseases to be 'close' in network space.

Jeremy K. Nicholson — Imperial College London. Founder of clinical metabonomics; brought metabolite fingerprinting into surgical and chronic-disease workflow.

Robert M. Sapolsky — Stanford University. The translator. His writing makes stress physiology legible to anyone with an eight-grade reading level and a curious mind.

Marieke Sonawane / Kimberly Glass — Harvard / Channing Lab. Built PANDA, SPIDER, and the family of gene regulatory network methods that took GRN inference from toy to tool.

Marc Vidal — Dana-Farber / Harvard. The interactome cartographer. Mapped large fractions of the human protein-protein interaction network at industrial scale.

Douglas C. Wallace — Children's Hospital of Philadelphia. Reframed metabolic and degenerative disease as fundamentally mitochondrial — a parallel network running alongside the nuclear one.

Your Notes

One page. Use it as you read. Redraw a diagram. Sketch a case.