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Lymphedema Symptom Science: Precision Phenotyping, Genotyping and Intervention

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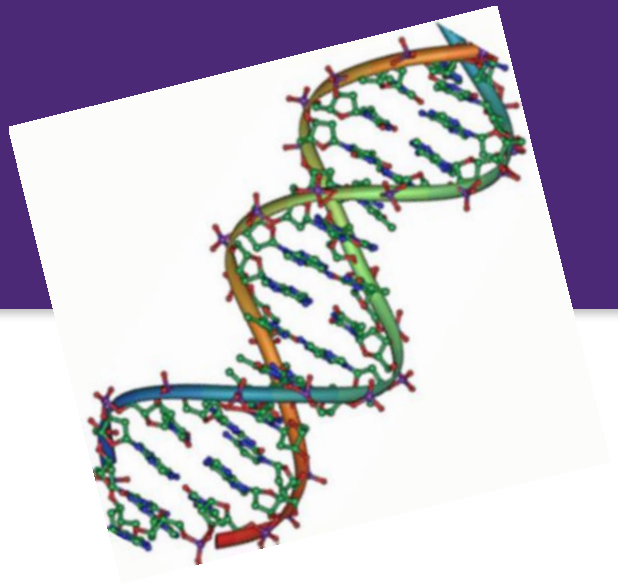
Associate Professor with Tenure



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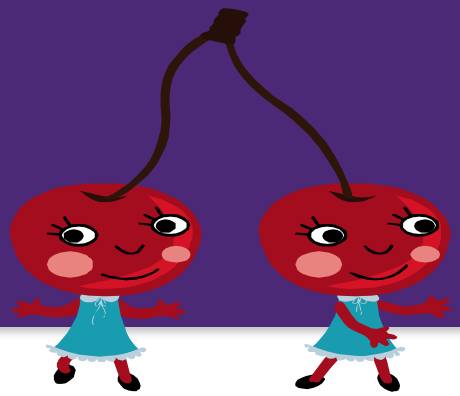
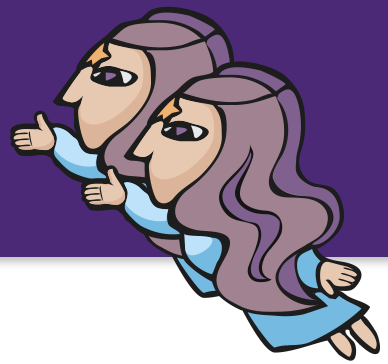
Learning Objectives

- The learner will be able to gain knowledge about different methods to conduct precision phenotyping.
- The learner will be able to gain knowledge about physiological and genetic/genomic approach to investigate the biological mechanism of lymphedema symptoms.
- The learner will be able to gain knowledge about developing precision intervention based on phenotyping characteristics and biological mechanism.

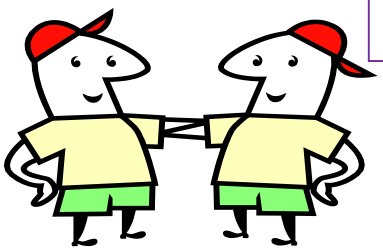


Phenotype



- The outward appearance of an individual
- The result of genetic inheritance and environment.

phenotyping — clinically characterizing traits that signify health or disease.



CANCER-RELATED LYMPHEDEMA

Approximately 28-40% of patients treated for gynecological cancer develop lymphedema.

Of the 3.1 million breast cancer survivors in the United States, approximately

20-40% of them have developed lymphedema.

Fu, M.R., Deng, J., Armer, J. (2014). Cancer-Related Lymphedema: Evolving Evidence for Treatment and Management from 2009 to 2014. *Clinical Journal of Oncology Nursing,* 18 (Supplement), 68-79. DOI: 10.1188/14.CJON.S3.68-79. PMID: 25427610.

What is LYMPHEDEMA ?

- Accumulation of lymph fluid in the interstitial spaces of the affected limb and areas
- Abnormality of or injuries to the lymphatic system

"With breast cancer, you go in for your treatment, once cancer is under control you are kind of done with it. With lymphedema, you will never be done with it because you are having this big arm, pain, burning, heaviness, and soreness every day. It's something that you have to live with for the rest of your life."

Mr. S, 7 years of lymphedema

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Fu, R.M. (2014). Breast cancer-related lymphedema: Symptoms, diagnosis, risk reduction, and management. *World Journal of Clinical Oncology*, 10;5(3):241-7. doi: 10.5306/wjco.v5.i3.241. PMID: 25114841

A great challenge for Precision Phenotyping of Lymphedema

- ✓ **The inconsistent criteria for diagnosis**
- ✓ **The use of various assessment methods**
- ✓ **Obesity, weight gain and increasing BMI**

Fu, M.R., Conley, Y.P., Axelrod, D., Amber, G.A., Yu, G., Fletcher, J., Zagzag, D. (2016). Precision assessment of heterogeneity of lymphedema phenotype, genotypes and risk prediction. *The Breast*. DOI: http://dx.doi.org/10.1016/j.breast.2016.06.023. Epub ahead print. PMID: 27460425

Water Displacement

- **A sensitive and accurate measure in the laboratory setting**
- **Limitations**:
  - ✓ Spillover and hygienic concerns.
  - ✓ Does not provide data about localization of the edema or shape of the extremity.
  - ✓ Contraindicated in patients with open skin lesions.
  - ✓ Patients may find it difficult to hold the position for the time needed for the tank overflow to drain.

Armer, J.M., & Stewart, B.R. (2005). A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphatic Research & Biology*, *3*(4), 208-217.

Sequential Circumference Limb Measurement

Armer, J.M., & Stewart, B.R. (2005). A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. *Lymphatic Research & Biology*, *3*(4), 208-217.

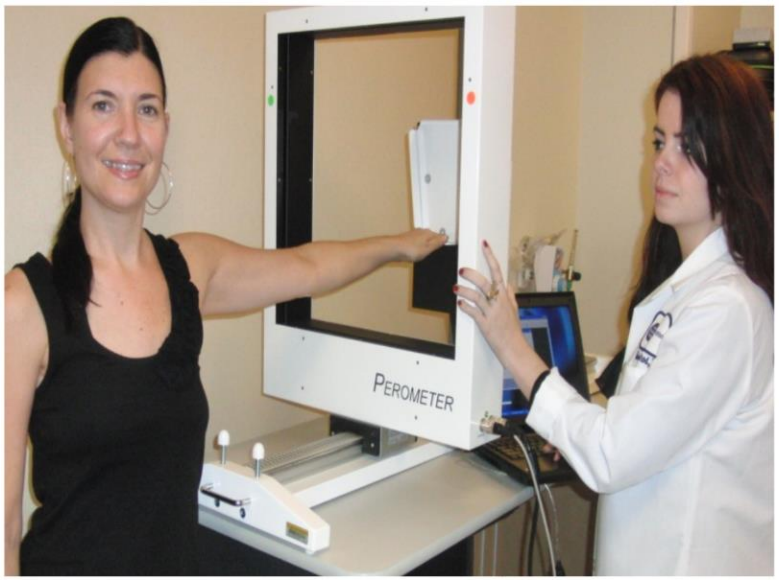
- **The most common criterion for diagnosis**:
  - ✓ ≥ 2 centimeters or ≥200 ml difference in limb volume as compared to the non-affected limb
  - ✓ 10% volume differences in the affected limb
- **Advantage**
  - ✓ **Cost-efficient???**
  - ✓ **Easily implemented in clinical settings???**
- **Limitations**
  - ✓ Time consuming
  - ✓ Difficulty in establishing inter- & intra-rater reliability

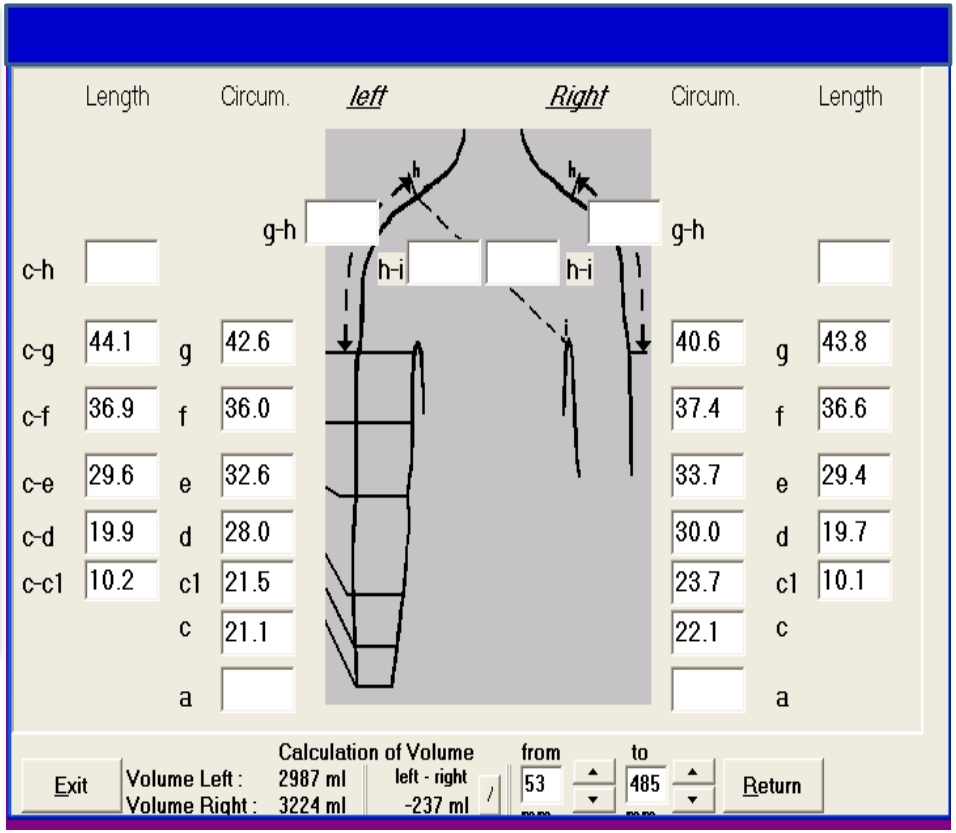
BIOIMPEDANCE ANALYSIS

The Imp XCA, a FDA approved device, uses a single frequency below 30 kHz to measure impedance and resistance of extracellular fluid.

Fu, M.R., Cleland, C.M., Guth, A.A., Kayal, M., Haber, J., Cartwright- Alcarese, F., Kleinman, R., Kang, Y., Scagliola, J., & Axelrod, D. (2013). L-Dex Ratio in Detecting Breast Cancer-Related Lymphedema: Reliability, Sensitivity, and Specificity. *Lymphology*, *46*(2)85-96.

Infra-Red Perometer Measurement





Fu, M.R., Axelrod, D., Guth, A., Cartwright- Alcarese, F.,Qiu, Z., Goldberg, J., Kim, J., Scagliola, J., Kleinman, R., Haber, J., & (2014). Proactive approach to lymphedema risk reduction: a prospective study. *Annals of Surgical Oncology, 21*(11), 3481-3498. Online First. DOI: 10.1245/s10434-014-3761-z

Symptoms?????

Cancer Related Symptoms:

- ***Subjective phenomenon***
- ***Indicates abnormal changes in body functioning or side effects from cancer treatment.***

Fu, M.R. & Rosedale, M. (2009). Breast cancer survivors' experience of lymphedema related symptoms. *Journal of Pain and Symptom Management*, *38*(6), 849-859. PMID: 19819668

Breast Cancer &Lymphedema Symptom Experience Index

The following questions are about your experiences with movement on your affected body side today or in the past three month. The word "affected" means the same body side(s) on which you received breast surgery or radiation.

On which body side was your cancer treated?
☐Right ☐Left ☐Both

Do you have limited movement of your affected___?	**How Severe?**				
	No 0	A little 1	Somewhat 2	Quite a bit 3	Very Severe 4
1. shoulder					
2. elbow					
3. wrist					
4. fingers					

The following questions are about symptoms in your affected arm, hand, breast, axilla (under arm), or chest today or in the past three month.

	How Severe?				
Have you had ___?	No 0	A little 1	Somewhat 2	Quite a bit 3	Very Severe 4
5. swelling					
6. breast swelling					
7. chest wall swelling					
8. firmness					
9. tightness					
10. heaviness					
11. toughness or thickness of skin					
12. stiffness					
13. tenderness					
14. hotness/increased temperature					
15. redness					
16. blistering					
17. pain					
18. numbness					
19. burning					
20. stabbing					
21. tingling					
22. arm or hand fatigue					
23. arm or hand weakness					
24. pocket of fluid develop					

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"An ontology is a specification of a conceptualization."
Tom Gruber, 1993

PHENOTYPE ONTOLOGY OF LYMPHEDEMA

A medical phenotype ontology describes the individual manifestations of diseases:

- ✓ signs & symptoms
- ✓ laboratory findings
- ✓ imaging studies, etc.

Deep phenotype: The precise and comprehensive analysis of phenotypic abnormalities.

PN Robinson (2012) Deep phenotyping for precision medicine. Hum Mutat 33: 777–780 (Special Issue of Human Mutation on Deep Phenotyping)

Bivariate Association Between Each Symptom and Lymphedema			
	Odds Ratio	95% CI	p-value
Arm Swelling	561.00	76.04 - 71644.49	<0.0001
Arm Heaviness	17.46	8.22 - 39.25	<0.0001
Arm Firmness	10.33	5.04 - 22.16	<0.0001
Increased Arm Temperature	9.07	2.98 - 29.94	0.0001
Seroma Formation	8.61	3.54 - 21.54	<0.0001
Arm Tightness	7.78	3.84 - 16.84	<0.0001
Limited Arm Movement	5.86	2.94 - 11.93	<0.0001
Tingling	5.54	2.79 - 11.26	<0.0001
Arm Aching	5.14	2.60 - 10.46	<0.0001
Limited Fingers Movement	4.56	1.92 - 10.66	0.0008
Limited Elbow Movement	4.39	1.53 - 12.21	0.0069
Limited Wrist Movement	4.23	1.58 - 10.99	0.0049
Limited Shoulder Movement	3.84	1.94 - 7.64	0.0001
Stiffness	3.55	1.75 - 7.16	0.0005
Burning	2.86	1.11 - 6.93	0.0299
Arm Redness	2.47	1.02 - 5.66	0.0450
Numbness	2.40	1.21 - 4.71	0.0124
Stabbing	2.12	0.92 - 4.64	0.0769
Tenderness	2.07	1.06 - 4.03	0.0320
Pain	1.99	1.01 - 3.89	0.0463
Arm Soreness	1.44	0.68 - 2.92	0.3285

A Syndrome Of Abnormal Swelling And Multiple Symptoms Due To The Accumulation Of Lymph Fluid.

* p<.05, **p<.01	Count of Symptoms 4-8 Weeks Post-op	Count of Symptoms 12 Months Post-op	Limb Volume Changes 4-8 Weeks Post-op	Limb Volume Changes 12 Months Post-op	L-Dex Ratio 4-8 Weeks Post-op	L-Dex Ratio 12 Months Post-op
Count of Symptoms 4-8 Weeks Post-op	1	0.334**	0.233**	0.343**	0.369**	0.309**
Count of Symptoms 12 Months Post-op	0.334**	1	0.309**	0.466**	0.356**	0.430**
Limb Volume Changes 4-8 Weeks Post-op	0.233**	0.309**	1	0.503**	0.352**	0.354**
Limb Volume Changes 12 Months Post-op	0.343**	0.466**	0.503**	1	0.454**	0.848**
L-Dex Ratio 4-8 Weeks Post-op	0.369**	0.356**	0.352**	0.454**	1	0.572
L-Dex Ratio 12 Months Post-op	0.309**	0.430**	0.354**	0.848**	0.572**	1

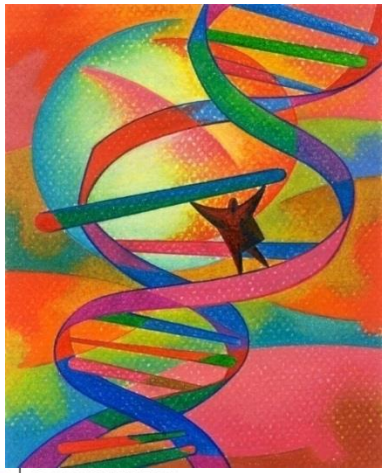
Symptoms	SYMPTOM CLUSTERS		
	Limb Mobility	Fluid Accumulation	Discomfort
Limited shoulder movement	.850		
Limited elbow movement	.742		
Limited wrist movement	.300	.331	
Limited fingers movement			.546
Limited arm movement	.852		
Hand swelling	N/A	N/A	N/A
Arm swelling		.627	
Breast swelling		.753	
Chest wall swelling		.688	
Arm firmness		.554	
Arm Tightness	.784		
Arm heaviness		.521	
Toughness or thickness of skin		.418	
Stiffness	.728		
Tenderness			.489
Hotness		.558	
Redness		.710	
Blister	N/A	N/A	N/A
Pain, aching, or soreness			.529
Numbness		.301	.321
Burning		.328	.556
Stabbing		.359	.694
Tingling			.466
Fatigue			.694
Weakness			

Precision Medicine
Precision Symptom Science

Precision medicine or precision health aims at discovering the right treatment, for the right patient, at the right time, as well as determination of factors contributing to or protecting from common and complex diseases.

So the Precision Medicine Initiative we're launching today will lay the foundation for a new generation of lifesaving discoveries.

--President Barack Obama
State of the Union Address, January 20, 2015



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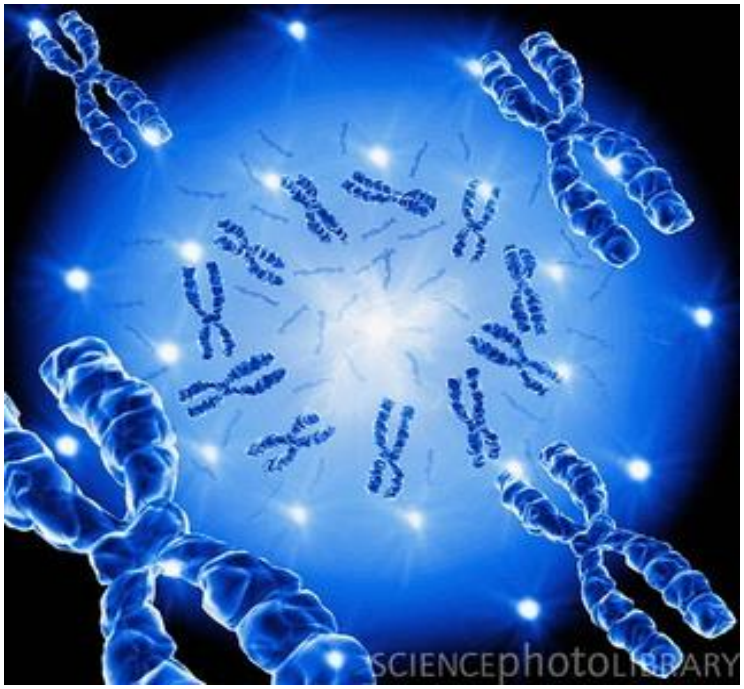
Precision Medicine

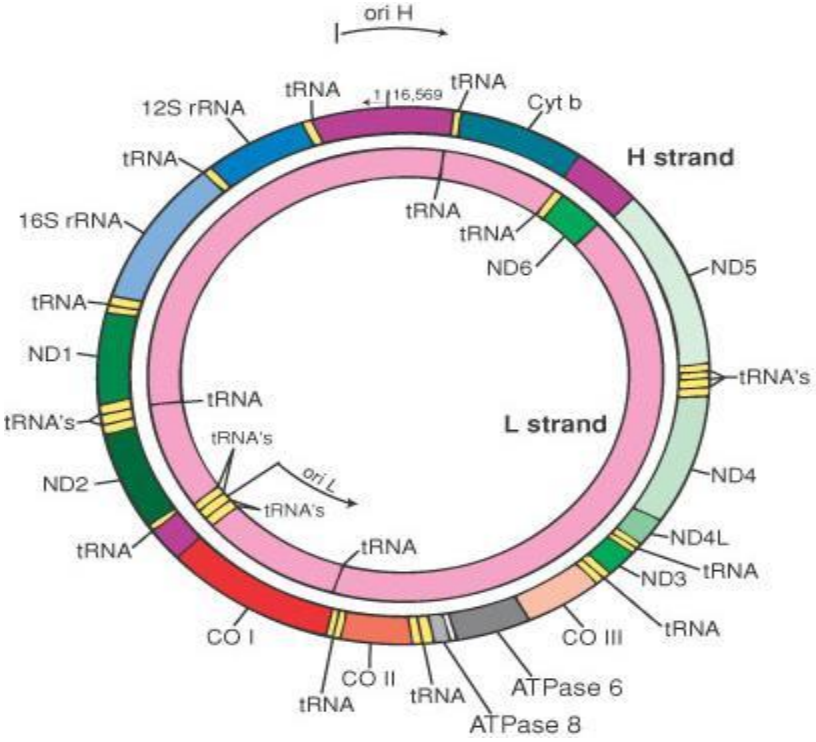
An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

Genotype

An individual's genetic constitution at a locus.

- The combination of the two sets of chromosomes (one from the egg, one from the sperm) that occurs at fertilization/conception
- Not always apparent/observable in a person





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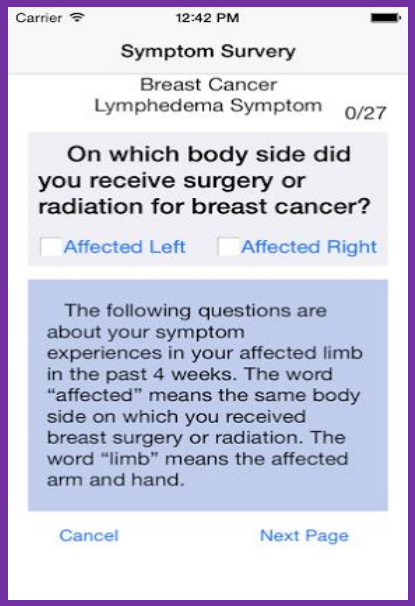
- No significant associations were found between arm lymphedema phenotype and any inflammatory genetic variations.
- IL1-*a* rs17561 was marginally associated with symptom count phenotype of ≥8 symptoms.
- IL-4 rs2070874 was significantly associated with phenotype of impaired limb mobility and fluid accumulation.
- Phenotype of fluid accumulation was significantly associated with IL6 rs1800795, IL4 rs2243250 and IL4 rs2070874.
- Phenotype of discomfort was significantly associated with VEGF-C rs3775203 and IL13 rs1800925.

Fu, M.R., Conley, Y.P., Axelrod, D., Amber, G.A., Yu, G., Fletcher, J., Zagzag, D. (2016). Precision assessment of heterogeneity of lymphedema phenotype, genotypes and risk prediction. *The Breast*. DOI: http://dx.doi.org/10.1016/j.breast.2016.06.023. Epub ahead print. PMID: 27460425

Genotype Additive Models			
Genotypes	**Phenotype of Fluid Accumulation**		
IL6 rs1800795 IL4 rs2070874 IL4 rs2243250	**No Fluid Accumulation (< 2 Symptoms)**	**Fluid Accumulation (2 + Symptoms)**	**P = 0.005 OR (95% CI)**
0	**41/54; 75.9%**	**31/64; 48.4%**	**1.00**
1	**10/54; 18.5%**	**18/64; 28.1%**	**2.38 (0.89 – 6.59)**
2	**3/54; 5.6%**	**12/64; 18.8%**	**5.29 (1.25 – 31.13)**
3	**0/54; 0.0%**	**3/64; 4.7%**	**-----**
Genotypes	**Phenotype of Pain and Discomfort**		
VEGF-C rs3775203 IL13 rs1800925	**No Discomfort (< 2 Symptoms)**	**Discomfort (2 + Symptoms)**	**P = 0.022 OR (95% CI)**
0	**6/17; 35.3%**	**14/93; 15.0%**	**1.00**
1	**10/17; 58.8%**	**49/93; 52.7%**	**2.10 (0.53 – 7.73)**
2	**1/17; 5.9%**	**30/93; 32.3%**	**12.86 (1.30 – 610.42)**

Global mHealth for Precision Assessment and Management of Lymphedema Symptoms: The-Optimal-Lymph-Flow™



Fu, M.R., Axelrod, D., Guth, A.A., Wang, Y., Scagliola, J., Hiotis, K., Rampertaap, K., El-Shammaa, N. (2016). Usability and Feasibility of Health IT Interventions to Enhance Self-Care for Lymphedema Symptom Management in Breast Cancer Survivors. *Internet Interventions 5, 56-64. DOI: http://dx.doi.org/10.1016/j.invent.2016.08.001*

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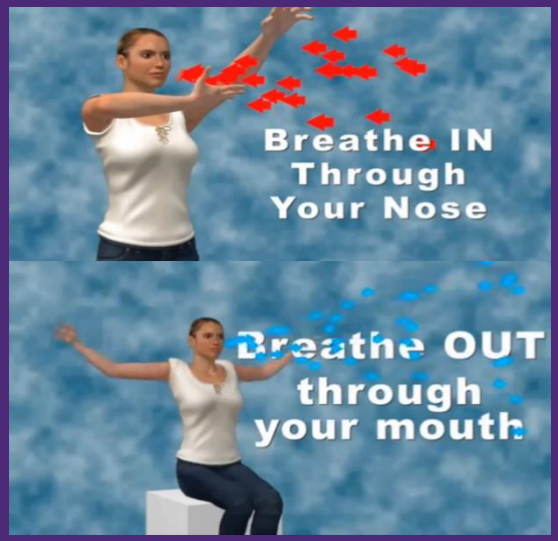
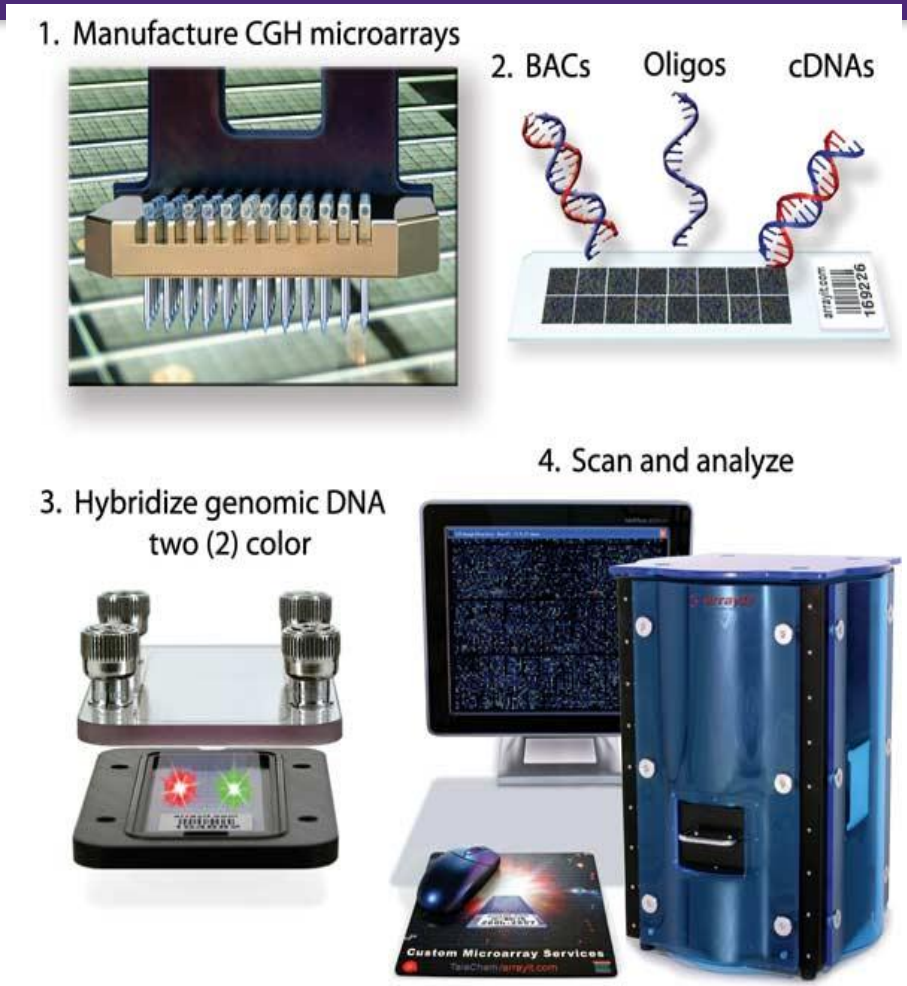
Improving early detection and intervention of lymphedema
PIs: Dr. Mei R. Fu
Dr. Yao Wang



The innovation of precision risk prediction and intervention will be hosted in *The-Optimal-Lymph-Flow* mHealth system (TOLF), a patient-centered, web-and-mobile-based educational and behavioral intervention focusing on safe, innovative, and pragmatic electronic assessment and self-care strategies for lymphedema symptoms.

FUTURE IMPLICATIONS

- Developing specific biomarker test
- Developing specific genomic test
- Machine Leaning for risk prediction
- Behavioral or pharmacological intervention might be developed targeting on the biomarkers



Precision Health Care