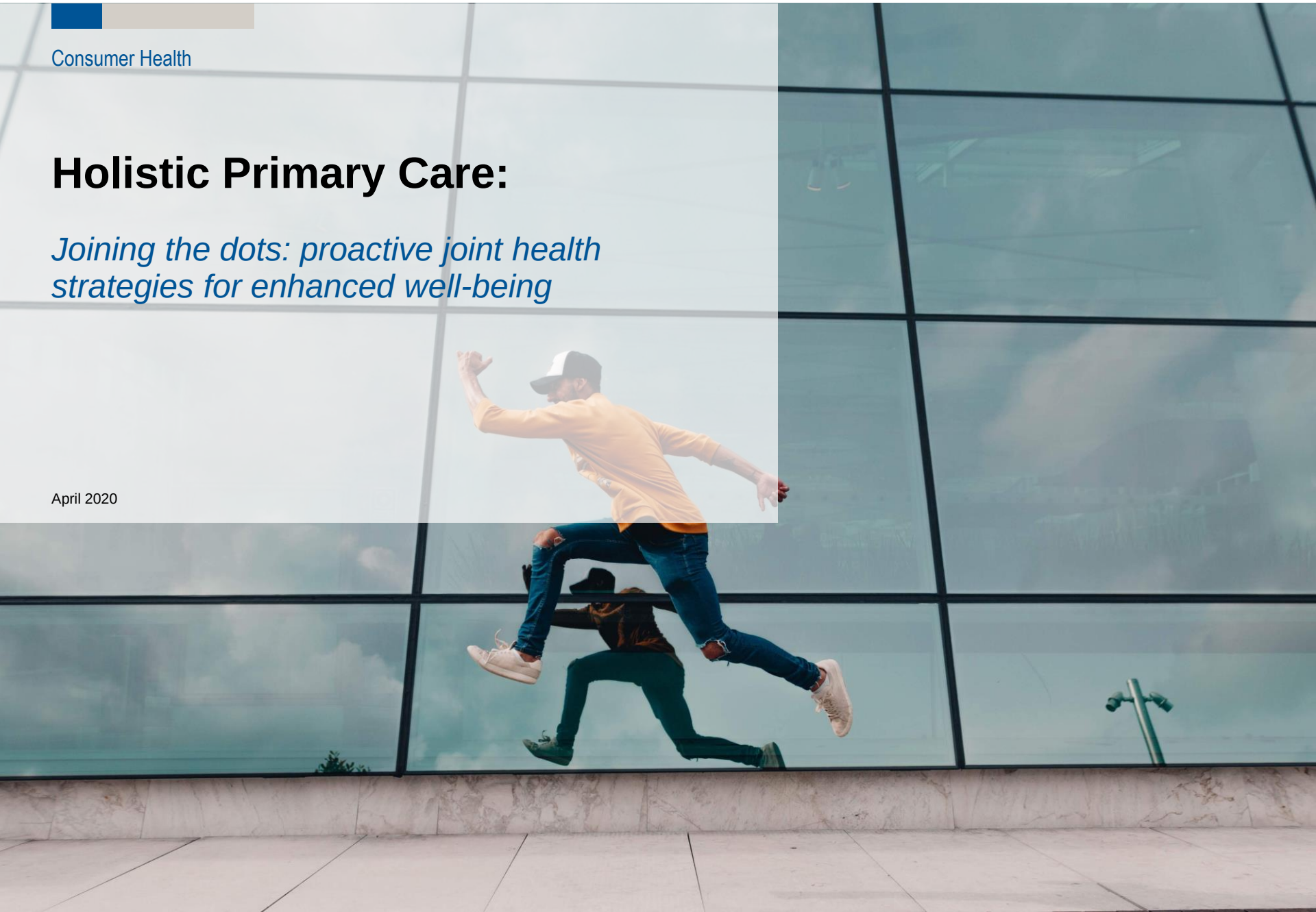
Lonza

Consumer Health

Holistic Primary Care:

Joining the dots: proactive joint health strategies for enhanced well-being



April 2020

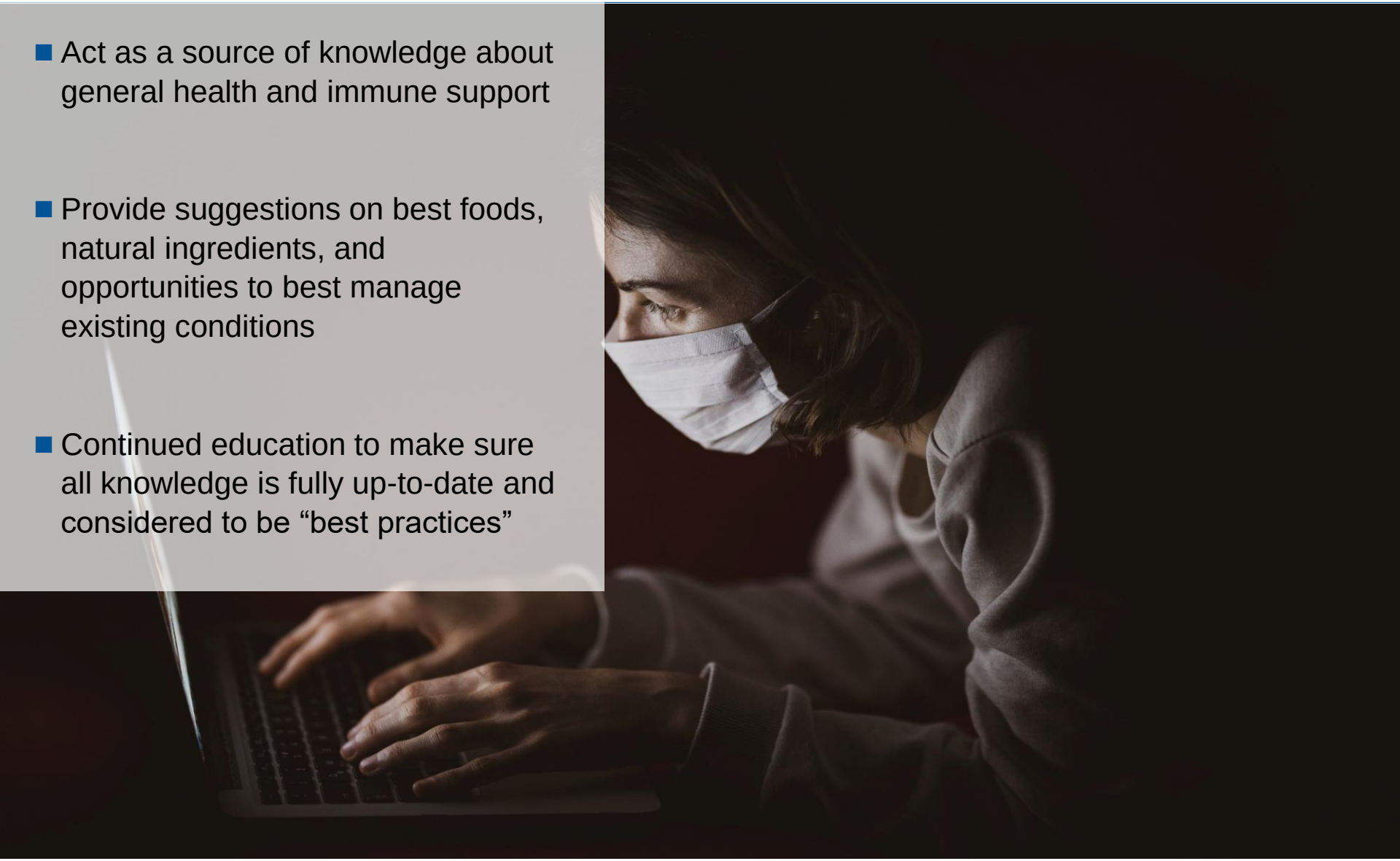
People Need Physician Support

- In difficult times, people look for insight and knowledge from trusted members of society
- Nurses, doctors, pharmacists, and health care practitioners ranked as the most trusted professions in America according to a Gallup polling
- Each of you have the opportunity to positively impact countless people over the upcoming months

Source: Honesty and Ethics Poll Gallup 2018

How Can We Provide Support?

- Act as a source of knowledge about general health and immune support
- Provide suggestions on best foods, natural ingredients, and opportunities to best manage existing conditions
- Continued education to make sure all knowledge is fully up-to-date and considered to be “best practices”

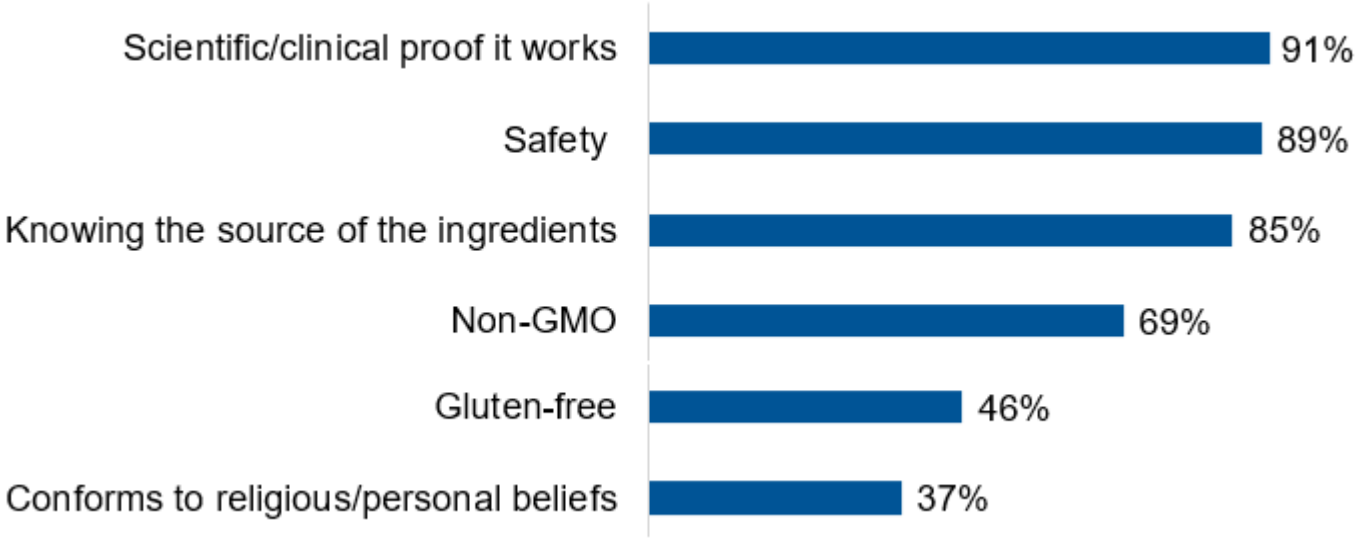


Consumer trust in medical professionals provides opportunity for dietary supplement education

- 78% of consumers agree that a doctor's recommendation plays an important role in their supplement purchasing decisions.
- Increased awareness of the benefits of natural, more natural & holistic health remedies provides medical professionals an opportunity to educate consumers on the importance of supplementation.

Source: 2018 NMI SORD Data

What are primary drivers people look for in dietary supplement purchases?



Science

Safety

Source

Source: Purchasing Values of Sports Nutrition Consumers 2018 NMI SORD Data

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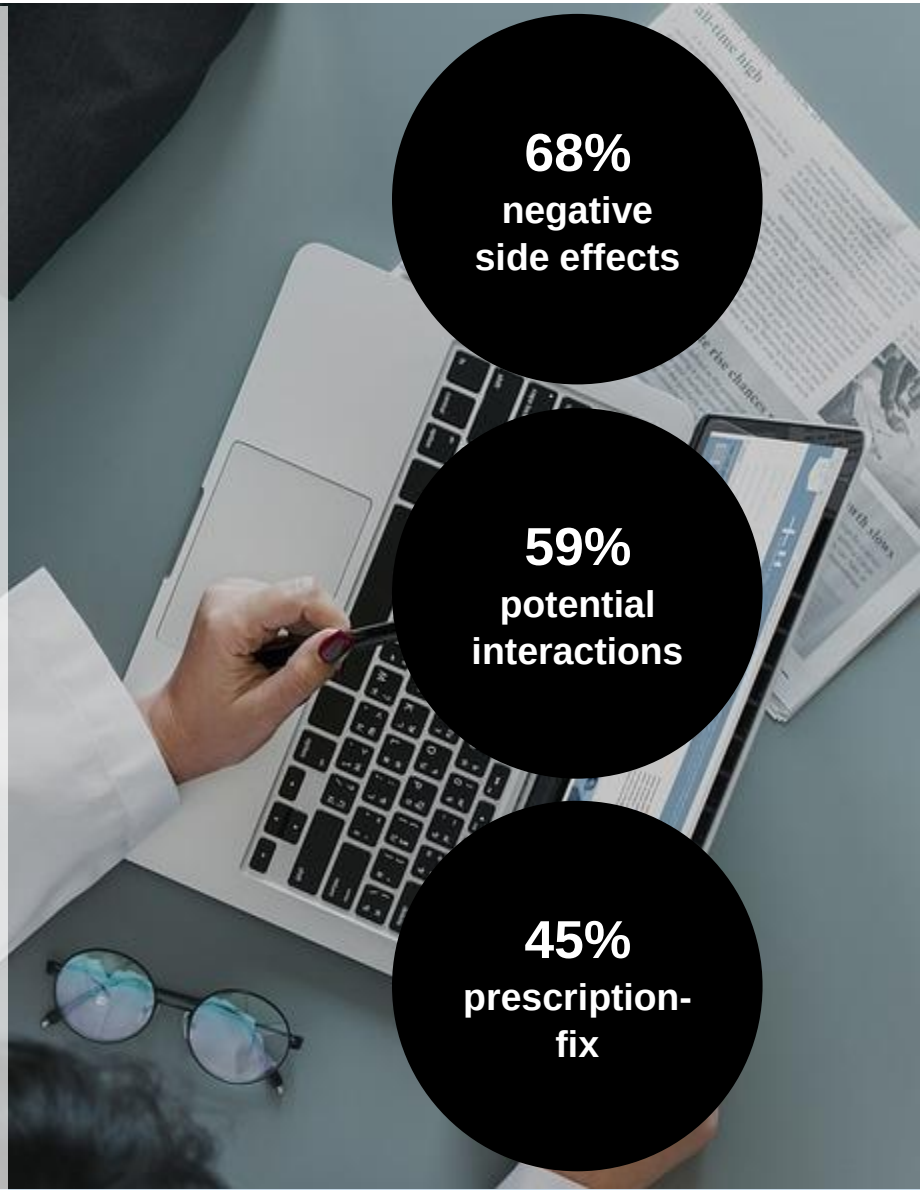
Consumer Health

What role do physicians play in consumer health decisions?

16 April 2020

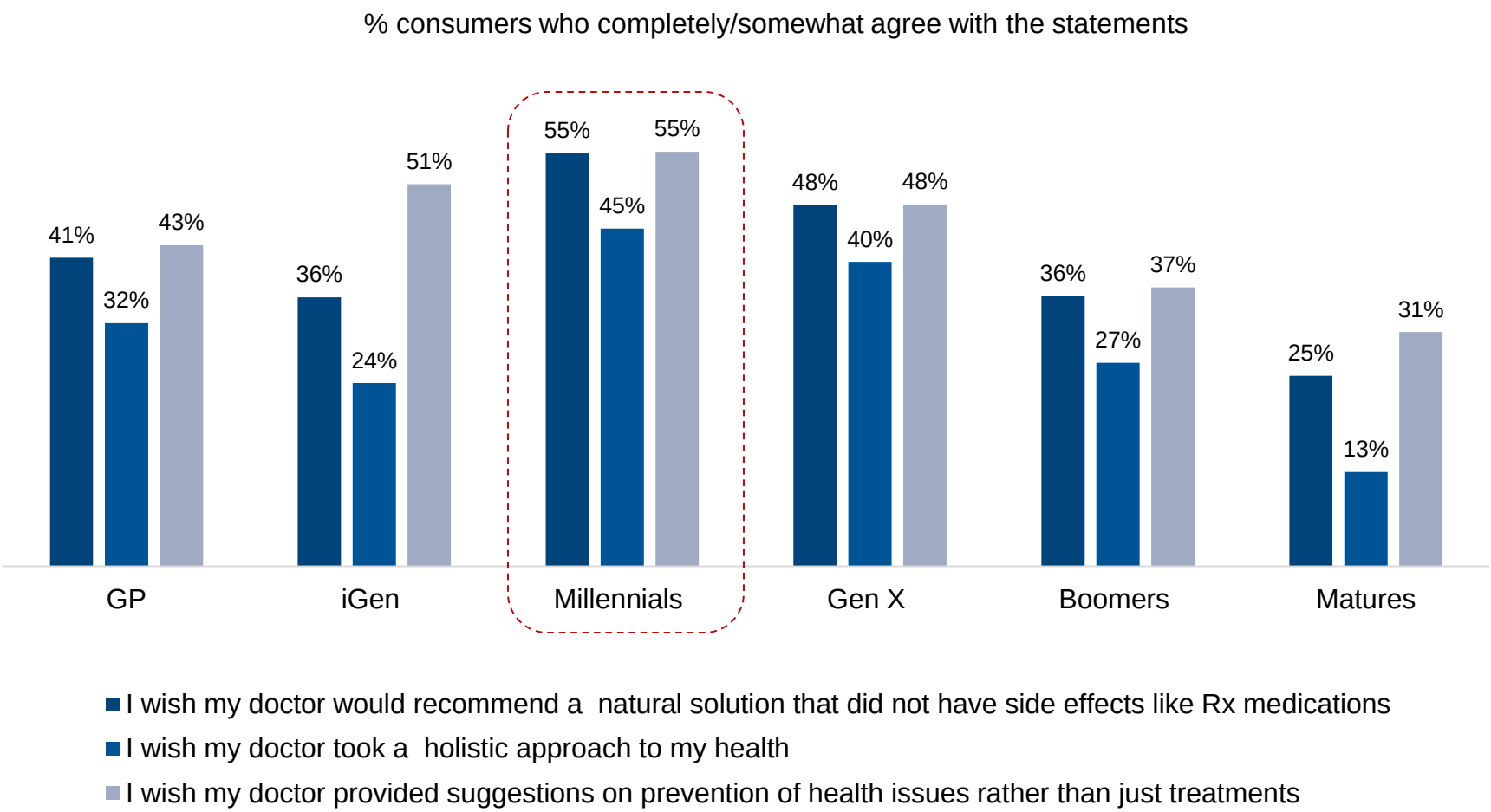
Consumer Concern of Prescriptions

- Over two thirds of consumers agree that they are concerned about negative side effects of prescription medications.
- Over half of consumers are concerned about potential interactions between prescription medications and supplements.
- Almost half of consumers feel that their doctors fall back on prescriptions in order to fix their health issues.
- Recent events have caused large increases in dietary supplement purchases…we must steer them to the right ingredients/products



Source: 2018 NMI SORD Data

But…consumers would like their doctors to recommend more natural solutions to their health issues. Millennials in particular are interested in more holistic and natural options.



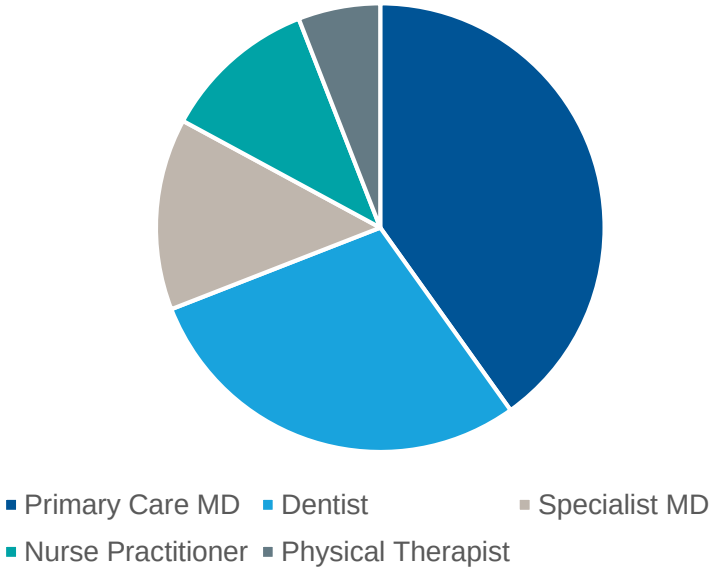
(Q.63- % consumers who completely/somewhat agree with the statements)
GP = general population, iGen = 5-22 years of age)

However, almost half of supplement users report that their doctors recommended that they use specific supplements.

% indicating their doctor has recommended that they use specific supplements

General Supplement User	**49%**
Light User (1-2/day)	45%
Medium User (2-5/day)	62%
Heavy User (6+/day)	61%

(Q.57a – TOP 5 % supplement users indicating which health professionals they have seen in the past year)



Source: 2018 NMI SORD Data

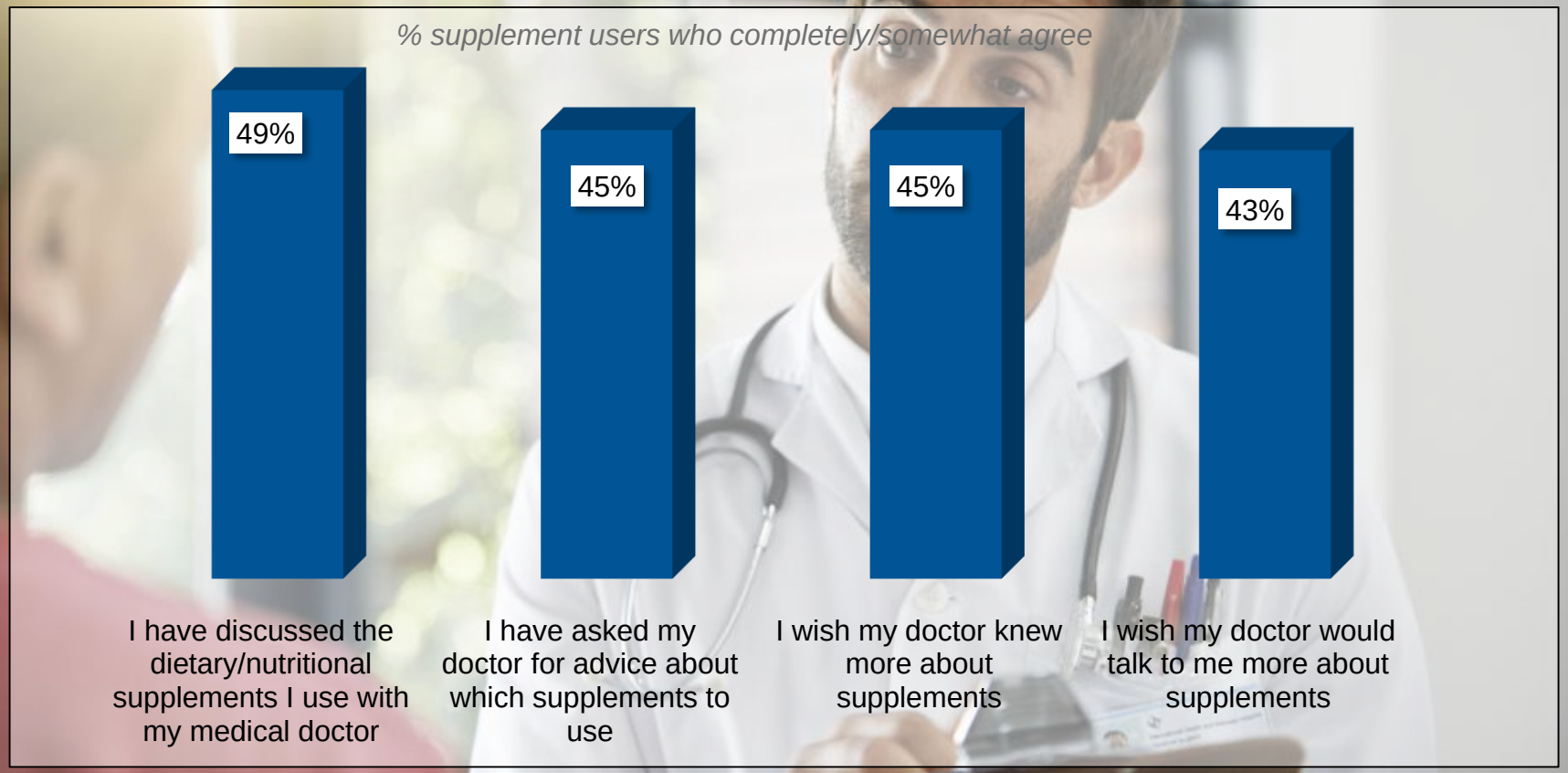
Consumers are most influenced by their physician when it comes to making decisions about supplementation

	Gen DS Pop	Millennials	Gen X	Boomer	Mature
Physician/Doctor	**90%**	**87%**	**90%**	**92%**	**95%**
Pharmacist	80%	80%	80%	80%	80%
Dietitian/Nutritionist	72%	79%	71%	67%	68%
Alternative healthcare practitioner	57%	71%	60%	45%	37%
Store personnel	51%	63%	50%	41%	36%
Health coach/personal trainer	51%	67%	50%	35%	35%

Source: 2018 NMI SORD Data

(Q.27 - % supplement users indicating the sources have a lot of influence on their decision to buy supplements)

Consumers indicate that there has been substantial discussion about supplements with their doctors.



(Q.29/Q.31/Q.33 - % supplement users who completely/somewhat agree with the statements/ % supplement users indicating they have done the following)

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Consumer Health

How can physicians leverage their influence on consumer supplementation decisions?

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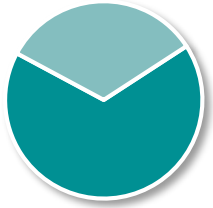
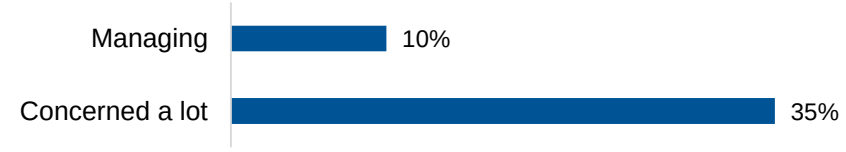
Understanding the levels of concern among likely users as well as the percentage of who are already managing the condition helps determine where the best opportunities exist.

% Likely Users of Supplements

Heart Likely	77%
Joint Likely	75%
Sports Likely	67%





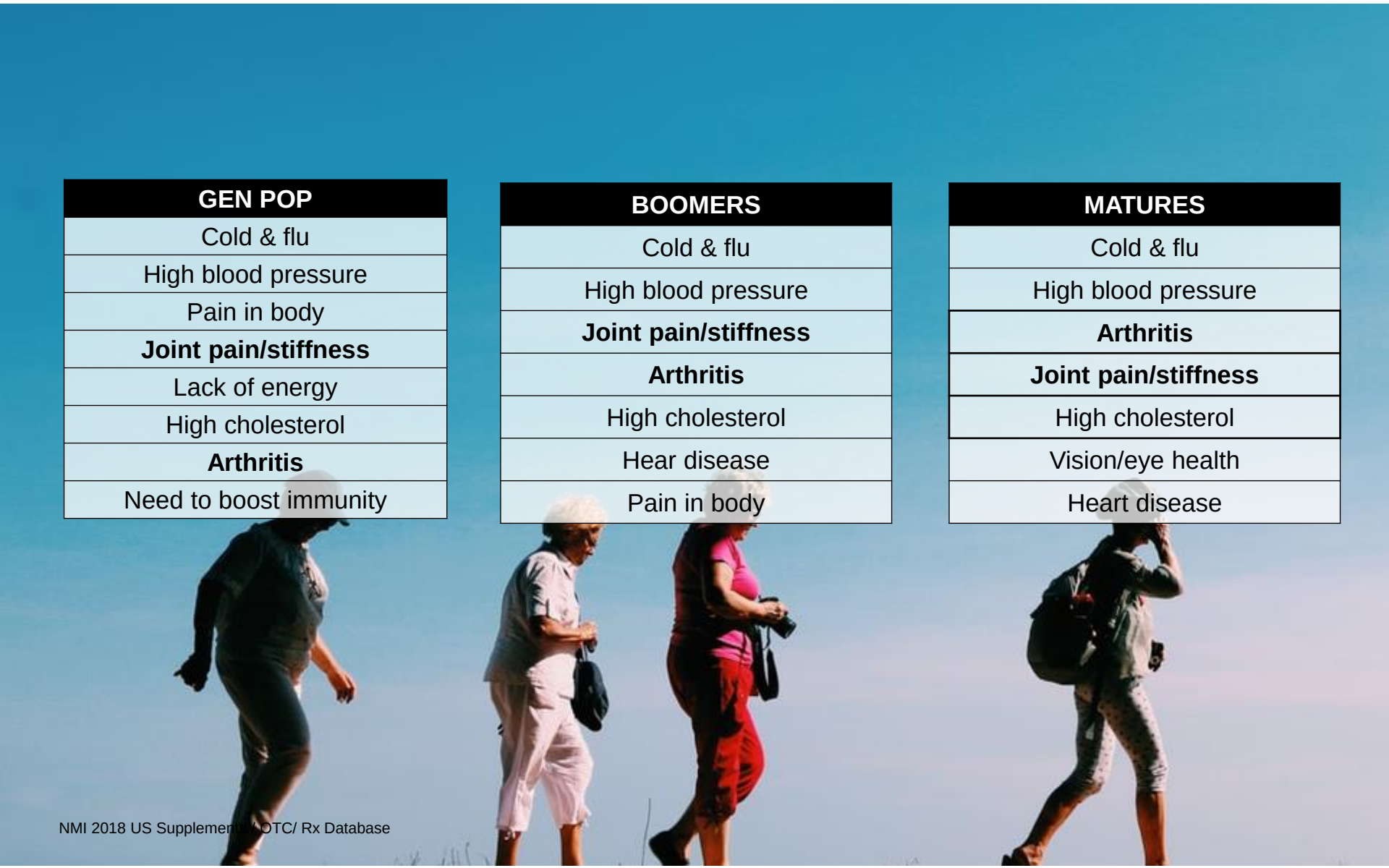
READ: 42% of Immune likely users are concerned a lot about preventing immune issues; 6% of Immune likely users are currently managing immune issues

Despite positive perceptions of effectiveness in joint health supplements, consumers across the generational segments continue to show high concern in this area.

GEN POP
Cold & flu
High blood pressure
Pain in body
Joint pain/stiffness
Lack of energy
High cholesterol
Arthritis
Need to boost immunity

BOOMERS
Cold & flu
High blood pressure
Joint pain/stiffness
Arthritis
High cholesterol
Hear disease
Pain in body

MATURES
Cold & flu
High blood pressure
Arthritis
Joint pain/stiffness
High cholesterol
Vision/eye health
Heart disease



NMI 2018 US Supplement OTC/ Rx Database

Consumers indicate strong opportunity for scientifically proven joint health supplements

- Nearly 75% of consumers would take a scientifically proven joint health supplement
- The majority of consumers turn to glucosamine + chondroitin as a joint health solution
- This ingredient combination requires consumers to take a large amount of pills/doses daily
- Research shows there is another class of ingredient which may provide superior support for joint health, along with more dosing strategies that support compliance

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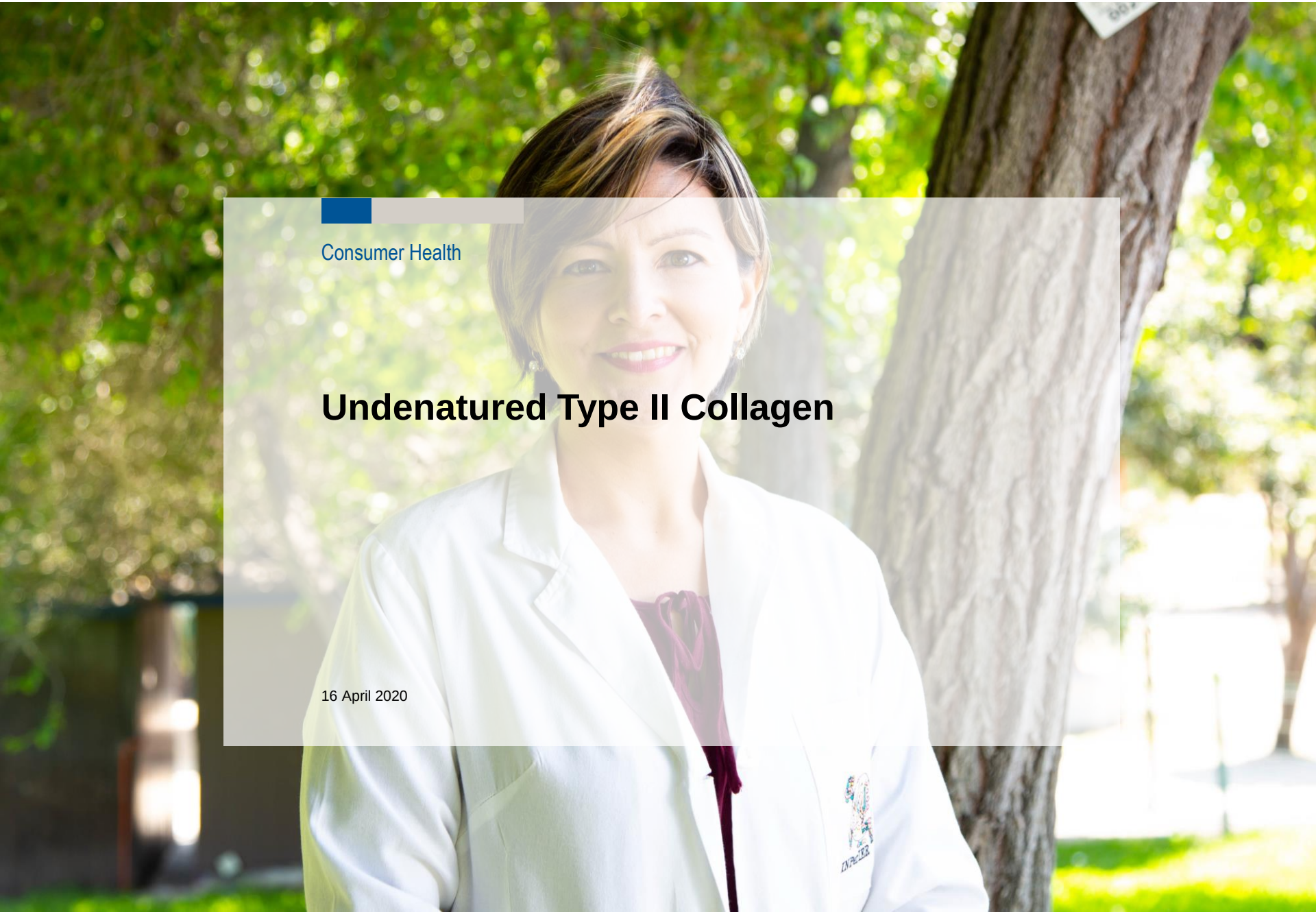
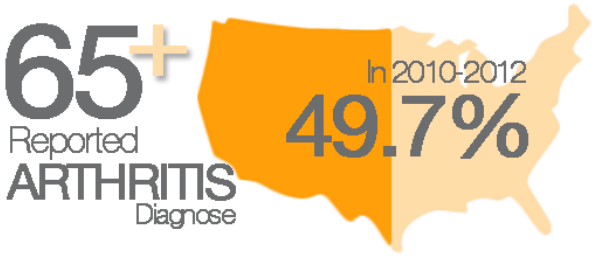


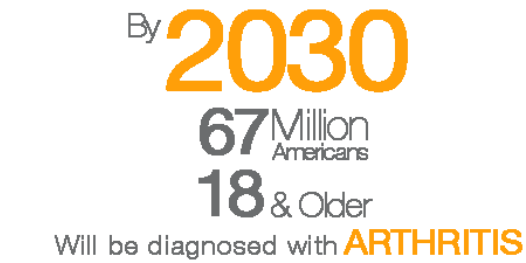
Consumer Health

Undenatured Type II Collagen

16 April 2020

Arthritis Statistics



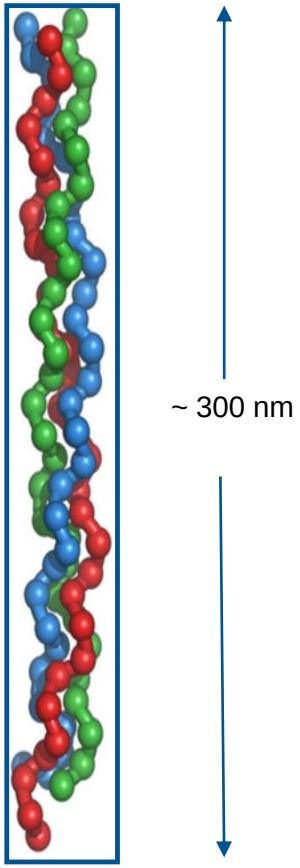


*Statistics provided by the Center for Disease Control and Prevention.

Undenatured type II collagen

The next step in joint support

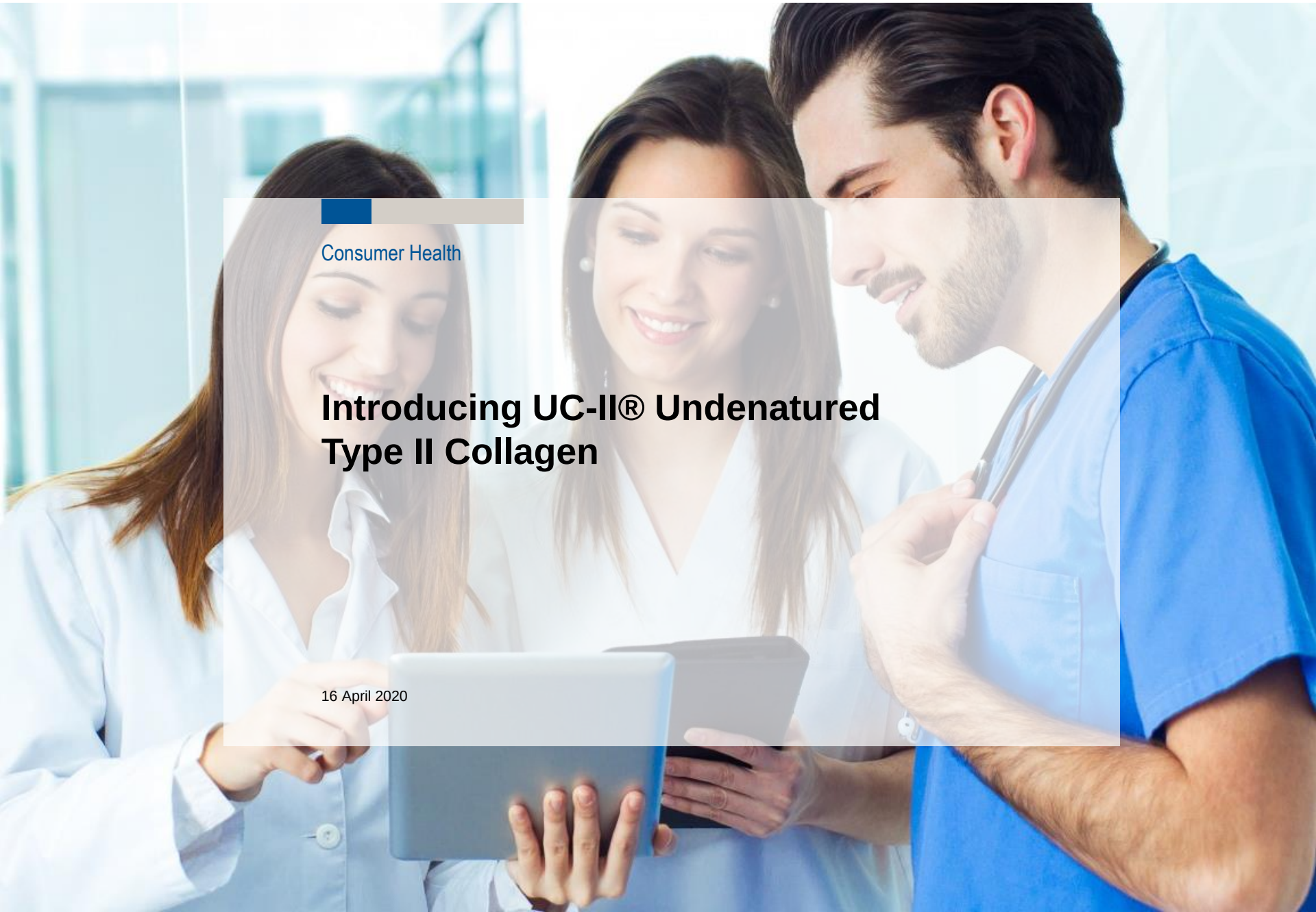
- Type II collagen is a protein that is part of cartilage, bone, and other tissues in animals and humans.
- Collagen naturally declines with age
- Undenatured (native) type II collagen is derived from chicken sternum cartilage
- Unique mechanism of action (Oral tolerance)
- Human clinical studies have found that just one 40 mg capsule of UC-II per day can help to promote joint comfort, as well as healthy joint function and flexibility



Collagen triple helix

UCII : Undenatured Type II Collagen, UCII®

K. Kuhn, 1987, in R. Mayne and R. Burgeson, eds., Structure and Function of Collagen Types, Academic Press, p. 2
Vander Rest M et al. *FASEB J.,* 1991, 5:2814.



Consumer Health

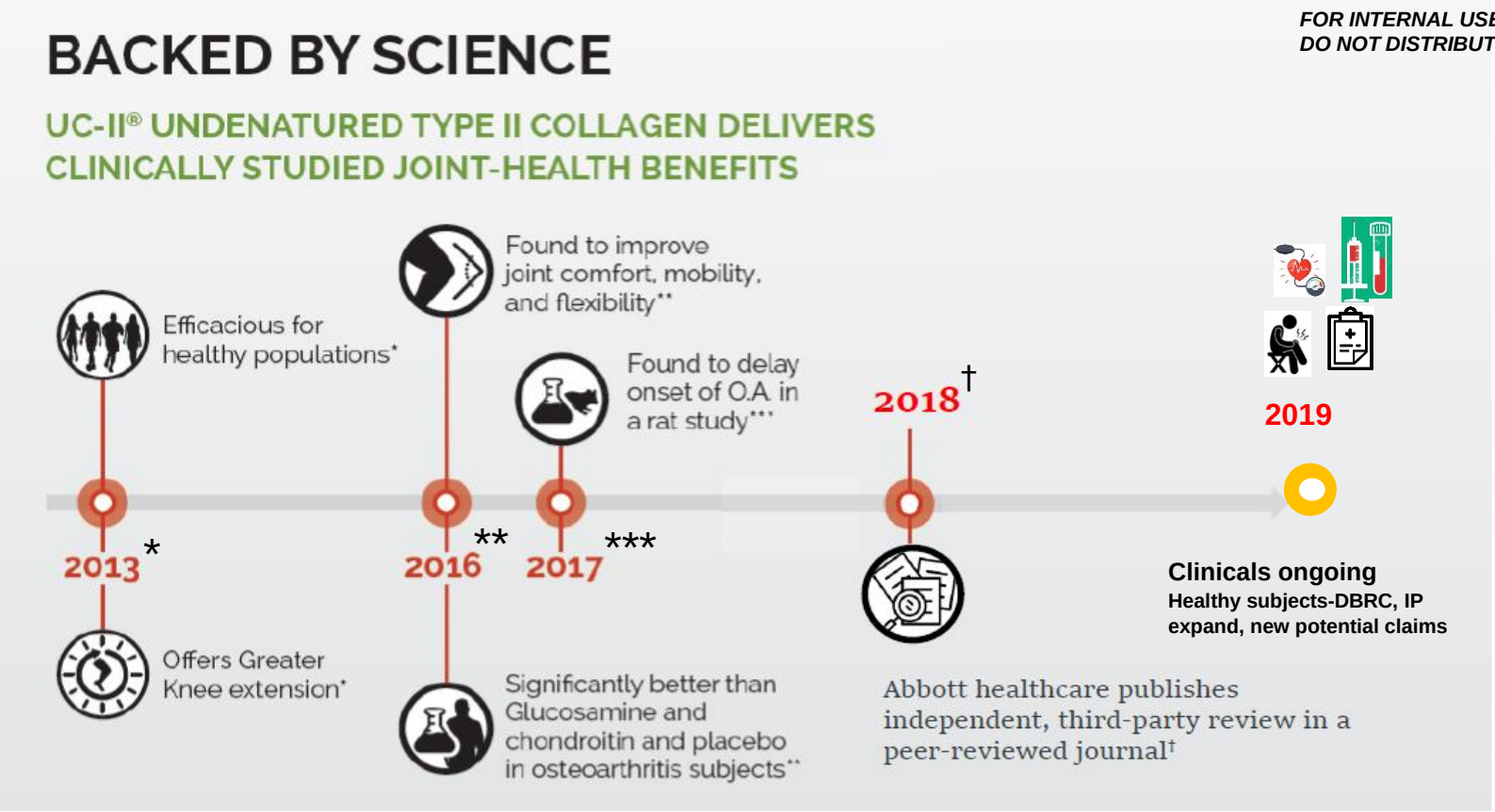
Introducing UC-II® Undenatured Type II Collagen

16 April 2020

History: UCII® Undenatured Type II Collagen

Science Backed History

FOR INTERNAL USE ONLY
DO NOT DISTRIBUTE



*Lugo JP, et al. *J Int Soc Sports Nutr*. 2013;10:48.
**Lugo JP, et al. *Nutr J*. 2016;15:14.
***Bagi, et al *Osteoarthritis cartilage*. 2017;12:2080-2090.
†Prabhoo R. *Int J Res Orthop*. 2018;4:684-689.

Summary : UCII studies (2013-2018)

Humans/Animals

Publication	Study design	Results
Humans		
Nutr J. 2016;15:14.	• OA Study : N = 186; Placebo ;GC (1500 mg G + 1200 mg C); UC-II® Brand (40 mg); Duration: 180- day study; Dose UCII: 40 mg	• ↓ Total WOMAC Score measures physical function, stiffness and pain in the knee • ↓ rescue medication compared to placebo and GC groups.
J Int Soc Sports Nutr. 2013;10:48	• HS Study: DBPRC; N = 55, Healthy Subjects; 40 mg Dose vs PLA; Duration: 120 d	• UC-II also demonstrated the potential to lengthen the period of pain free strenuous exertion and alleviate the joint pain • Well tolerated and led to improved knee joint extension in healthy subjects
Int J Med Sci. 2009 Oct 9;6(6):312-21.	• N=52; 40 mg UC-II containing 10 mg of bioactive undenatured type II collagen; Duration: 90 d	• ↓ WOMAC score by 33% as compared to 14% in G+C treated group • ↓ VAS score by 40% after 90 days as compared to 15.4% in G+C treated group • ↓ Lequesne's functional index score by 20% as compared to 6% in G+C treated group
Int J Clin Pharmacol Res. 2002;22(3-4):101-10.	• A pilot study was conducted for 42 days to evaluate the efficacy of UC-II (10 mg/day) in five female subjects (58-78 years) suffering from significant joint pain	• ↓ pain including morning stiffness, stiffness following periods of rest, pain that worsens with use of the affected joint and loss of joint range of motion and function was observed
Animals		
J Med Food. 2013 Nov;16(11):1039-45.	• Mice: collagen-induced arthritis (CIA);	• Suppression of CIA by inducing CD4+CD25+ Treg cells. ↓ The arthritis index , ↓ Serum IL-6 levels , ↑serum IL-2 level • Enhanced the proportion of CD4+CD25+T (Treg) cells, and gene expressions of stimulated dendritic cells induced markers for regulatory T cells such as forkhead box p3 (Foxp3), transforming growth factor (TGF)-β1, and CD25.
Osteoarthritis Cartilage. 2017 Dec;25(12):2080-2090	• N- 20 male rats ; subjected to partial medial meniscectomy tear (PMMT) surgery to induce OA. Oral daily dose of UC-II at 0.66 mg/kg for a period of 8 weeks.	• improve the mechanical function of the injured knee and prevent excessive deterioration of articular cartilage.
J Vet Pharmacol Ther. 2009 Dec;32(6):577-84. doi: 10.1111/j.1365-2885.2009.01079.x. []	• Horses:placebo, undenatured type II collagen (UC-II) at 320, 480, or 640 mg (providing 80, 120, and 160 mg active UC-II, respectively), and glucosamine and chondroitin (5.4 and 1.8 g, respectively, bid for the first month, and thereafter once daily) for 150 days	• 320 or 480 or 640 mg UC-II exhibited significant reduction in arthritic pain ($P < 0.05$). Well tolerated; No AEs.
Toxicol Mech Methods. 2007;17:189-196. *J. Anim. Physiol. Anim. Nutr.* 2012;96:770-777	• Twenty OA dogs divided into four groups (n = 5) were daily treated orally for 120 days: group I, placebo; group II, 10 mg UC-II; group III, 2,000 mg glucosamine + 1,600 mg chondroitin; group IV, UC-II (10 mg) + glucosamine (2,000 mg) + chondroitin (1,600 mg), followed by a 30-day withdrawal period • Dogs in four groups (n = 7-10), were treated daily for a period of 150 days with placebo (Group-I), 10 mg active UC-II (Group-II), 2000 mg GLU + 1600 mg CHO (Group-III), and UC-II + GLU + CHO (Group-IV).	• Daily treatment of arthritic dogs with UC-II alone or in combination with glucosamine and chondroitin markedly alleviates arthritic-associated pain. Well tolerated.No AEs • Moderately arthritic dogs treated with UC-II (10 mg) showed a marked reduction in arthritic pain with maximum improvement by day 150. Well tolerated, NO AEs.

UCII : Undenatured Type II Collagen, UCII®

Osteoarthritis (OA) Study, 2016

Randomized, Double-Blind, Placebo-Controlled Study

Lugo *et al. Nutrition Journal* (2016) 15:14
DOI 10.1186/s12937-016-0130-8

Nutrition Journal

RESEARCH Open Access

Efficacy and tolerability of an undenatured type II collagen supplement in modulating knee osteoarthritis symptoms: a multicenter randomized, double-blind, placebo-controlled study

James P. Lugo[1], Zainulabedin M. Saiyed[1] and Nancy E. Lane[2*]

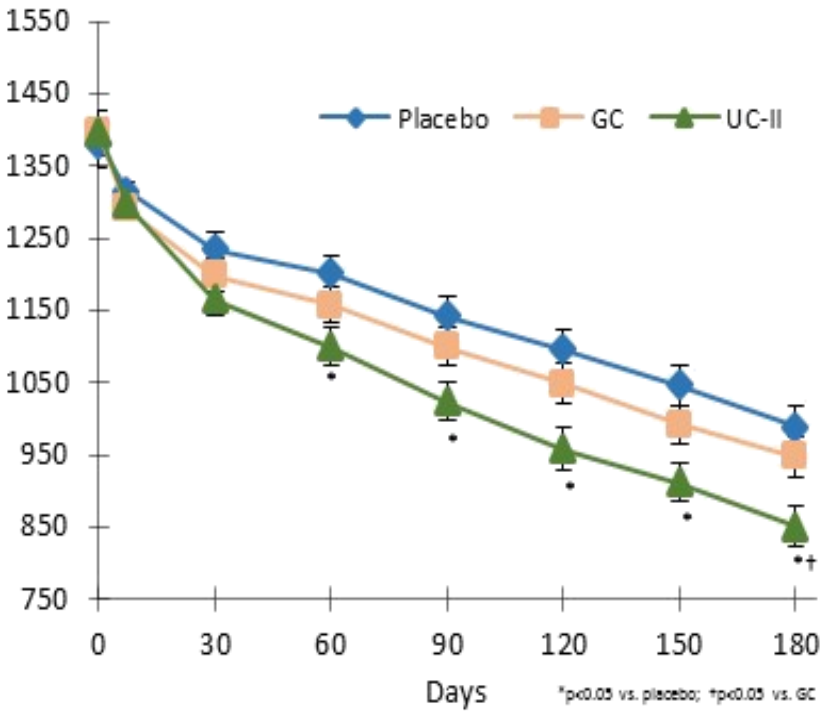
Undenatured Type II Collagen ↓ Total WOMAC Score

Randomized, Double-Blind, Placebo-Controlled Study

Study Design	
3 Groups	Placebo GC (1500 mg G + 1200 mg C) UC-II® Brand (40 mg)
Subjects	N = 186
Age	40–75
Primary Endpoint	Change in Total WOMAC at Day 180 vs PBO & GC
Secondary Endpoints	Mean VAS, LFI and WOMAC Subscales at Day 180 vs PBO & GC
Visits	Days 0, 7, 30, 60, 90, 120, 150 & 180
Population	Osteoarthritic subjects (Moderate to severe)
# Centers	13 clinics participated in study

Total WOMAC Score measures physical function, stiffness and pain in the knee

Total WOMAC Score Reduction

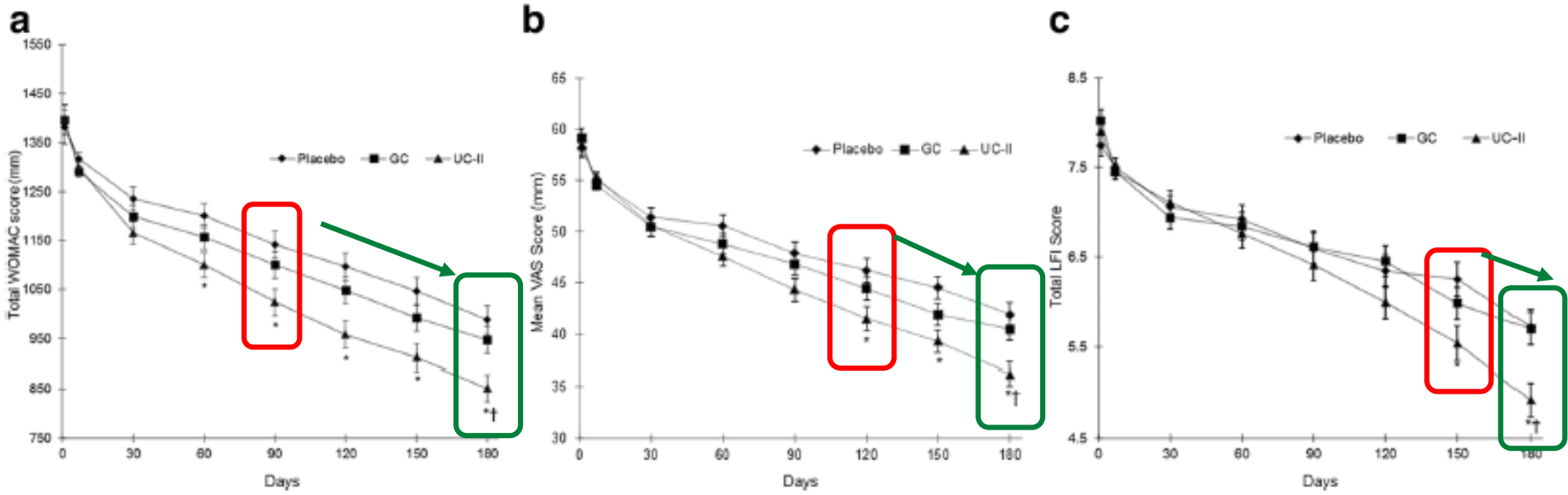


- Statistically significantly more effective than GC as measured by WOMAC

Nutr J. 2016;15:14.

UCII : Undenatured Type II Collagen, UCII®

UCII Supplementation ↓Total WOMAC Score, ↓VAS Pain Score and ↓ Total LFI score



Total WOMAC score (**a**), Mean VAS (**b**), Total LFI (**c**) in the UC-II, GC and placebo groups over the 180-day study period. Values are presented as mean ± SE. *Significant difference between the UC-II ($n = 54$) and the placebo ($n = 53$) group, $p < 0.05$. †Significant difference between the UC-II ($n = 54$) and the GC group ($n = 57$), $p < 0.05$

Lequesne's Algofunctional Index (**LFI**) **score**

UCII : Undenatured Type II Collagen, UCII®

WOMAC Subscales

Parameter reduction	Day	Placebo ($n = 53$)	GC ($n = 57$)	UC-II ($n = 54$)	p value			
					Overall[a]	GC vs PBO	UC-II vs PBO[b]	UC-II vs GC[c]
WOMAC pain	7	3.21 ± 0.58	4.57 ± 0.54	3.88 ± 0.55	-	-	-	-
	30	6.61 ± 1.04	7.89 ± 1.00	9.18 ± 1.01	-	-	-	-
	60	8.17 ± 1.10	10.1 ± 1.07	12.7 ± 1.09	0.0149	-	0.011	-
	90	11.2 ± 1.17	12.7 ± 1.14	16.4 ± 1.16	0.0063	-	0.0059	-
	120	12.9 ± 1.28	15.6 ± 1.22	19.9 ± 1.26	0.0005	-	0.0004	0.040
	150	15.0 ± 1.21	17.5 ± 1.16	21.5 ± 1.20	0.0007	-	0.0006	0.047
	180	17.0 ± 1.25	19.2 ± 1.20	24.0 ± 1.23	0.0003	-	0.0003	0.016
WOMAC stiffness	7	3.47 ± 0.64	4.22 ± 0.61	4.24 ± 0.62	-	-	-	-
	30	6.81 ± 1.10	8.76 ± 1.05	9.28 ± 1.07	-	-	-	-
	60	9.36 ± 1.28	11.5 ± 1.25	13.1 ± 1.27	-	-	-	-
	90	11.3 ± 1.36	13.8 ± 1.32	17.0 ± 1.35	0.0158	-	0.010	-
	120	13.6 ± 1.40	15.0 ± 1.34	20.0 ± 1.39	0.0035	-	0.0039	0.029
	150	15.5 ± 1.32	17.7 ± 1.26	21.3 ± 1.31	0.0079	-	0.0058	-
	180	17.8 ± 1.31	19.4 ± 1.27	23.8 ± 1.30	0.0043	-	0.004	0.044
WOMAC physical function	7	3.17 ± 0.56	4.14 ± 0.53	3.91 ± 0.53	-	-	-	-
	30	6.30 ± 1.00	7.80 ± 0.96	9.26 ± 0.98	-	-	-	-
	60	7.75 ± 1.08	9.50 ± 1.05	11.9 ± 1.07	0.0278	-	0.020	-
	90	10.4 ± 1.17	12.1 ± 1.14	15.1 ± 1.16	0.0182	-	0.0136	-
	120	12.7 ± 1.20	14.5 ± 1.15	17.9 ± 1.19	0.0083	-	0.0064	-
	150	14.8 ± 1.19	16.9 ± 1.14	20.0 ± 1.18	0.0078	-	0.006	-
	180	17.3 ± 1.21	18.8 ± 1.16	22.5 ± 1.20	0.0068	-	0.007	-

Values presented as Mean ± SE

[a]Overall p value was obtained by comparing the mean changes among the three groups using ANCOVA

[b]Significant difference between the UC-II and the placebo groups using Tukey-Kramer test

[c]Significant difference between the UC-II and the GC groups using Tukey-Kramer test, '-'denotes a non-significant statistical outcome

UCII : Undenatured Type II Collagen, UC-II®

Number of Subjects Using Rescue Medication ↓ in UC-II Supplementation Group

Day	Placebo	GC	UC-II
7	11/58	12/65	3/63
30	18/58	7/63	4/61
60	12/58	9/61	6/59
90	12/56	8/59	3/57
120	13/54	13/59	7/55
150	10/54	12/59	3/55
180	11/53	7/57	4/54
Entire study period	28/58	21/65	11/63*

The table summarizes the number of unique individuals reporting the use of rescue medication. Data presented as number of subjects using rescue medication / total number of subjects observed. *statistically significant versus the placebo (p=0.001) based on pairwise Tukey-Kramer multiple comparison test. The overall group effect p-value was 0.002 using logistic regression.

UCII : Undenatured Type II Collagen, UCII®

Nutr J. 2016;15:14.

Key Outcomes from 2016 OA Study

Randomized, Double-Blind, Placebo-Controlled Study

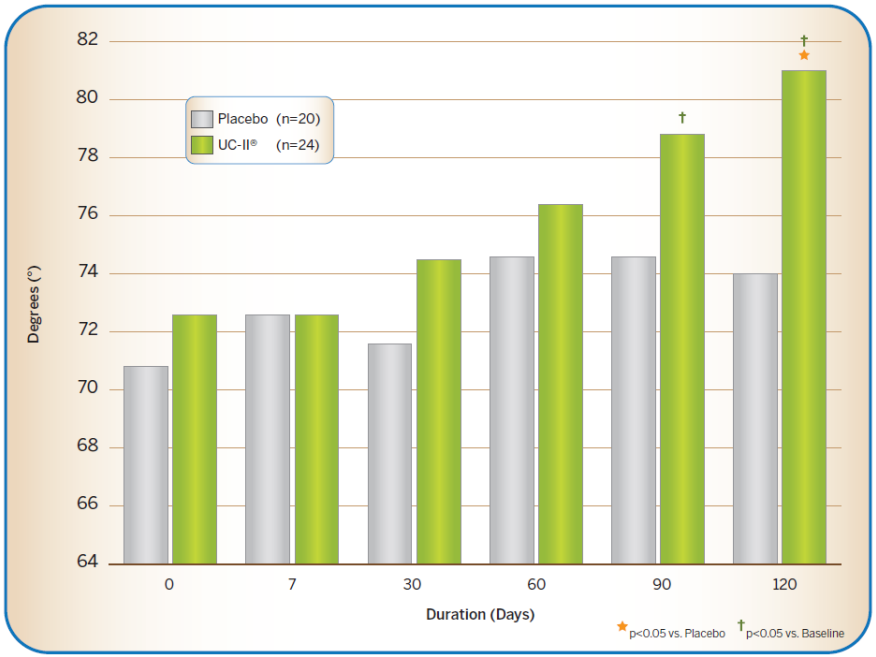
- UC-II achieved statistical significance versus placebo
- UC-II achieved statistical significance versus GC
- GC failed to achieve significance versus placebo

UCII : Undenatured Type II Collagen, UCII®

Healthy Subject Study, 2013

Randomized, Double-Blind, Placebo-Controlled Study

Study Design	
Groups	Group 1: UC-II, 40 mg Group 2: Placebo
Subjects	N=55
Age	≥ 30 -≤65 y
Duration	120 Days
Primary Endpoint	Improvement in knee function (ROM)
Secondary Endpoints	Time to **onset** of knee joint pain on Stepmill Time to **offset** of knee joint pain after stepping off the Stepmill
Time Points Measured	0, 7, 30, 60, 90 and 120 days
Average Age of Subjects	46 years



- Subjects taking UC-II® brand undenatured type II collagen significantly increased their knee extension range compared to placebo

J Int Soc Sports Nutr. 2013;10:48

UCII : Undenatured Type II Collagen, UCII®

Subjects Reporting Loss of Knee Pain in UCII Supplementation Group

Visit	UC-II			Placebo		
	No. of pain free subjects (%)	Continuity of pain loss[#]	P value (Binomial test)	No. of pain free subjects (%)	Continuity of pain loss[#]	P value (Binomial test)
Baseline	0.0 (0)	0	NA	0.0 (0)	0	NA
Day 7	0.0 (0)	0	NA	0.0 (0)	0	NA
Day 30	1.0 (4)	1N	0.5	0.0 (0)	0	NA
Day 60	3.0 (13)	1R, 2N	0.125	0.0 (0)	0	NA
Day 90	3.0 (13)	2R, 1N	0.125	1 (5)	1N	0.5
Day 120	5.0 (21)	3R, 2N	0.031[†]	1 (5)	1R	0.5

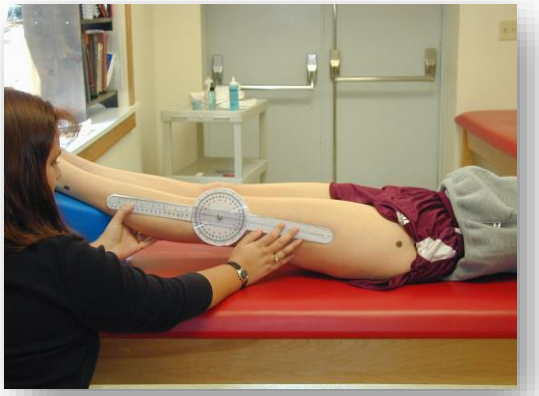
Continuity indicates the number of subjects in whom the absence of pain was maintained across visits. [†]Significant at $p \leq 0.05$ based on independent binomial testing of each visit using the null hypothesis that the probability of a subject experiencing no joint pain is equal to zero. [#]*R* Repeat subject (i.e. same subject who reported no pain in previous visit), *N* New subject who reports no pain for the first time.

UCII : Undenatured Type II Collagen, UCII®

Key Outcomes of Healthy Subject Study

The Benefits Seen from the Healthy Subject Study

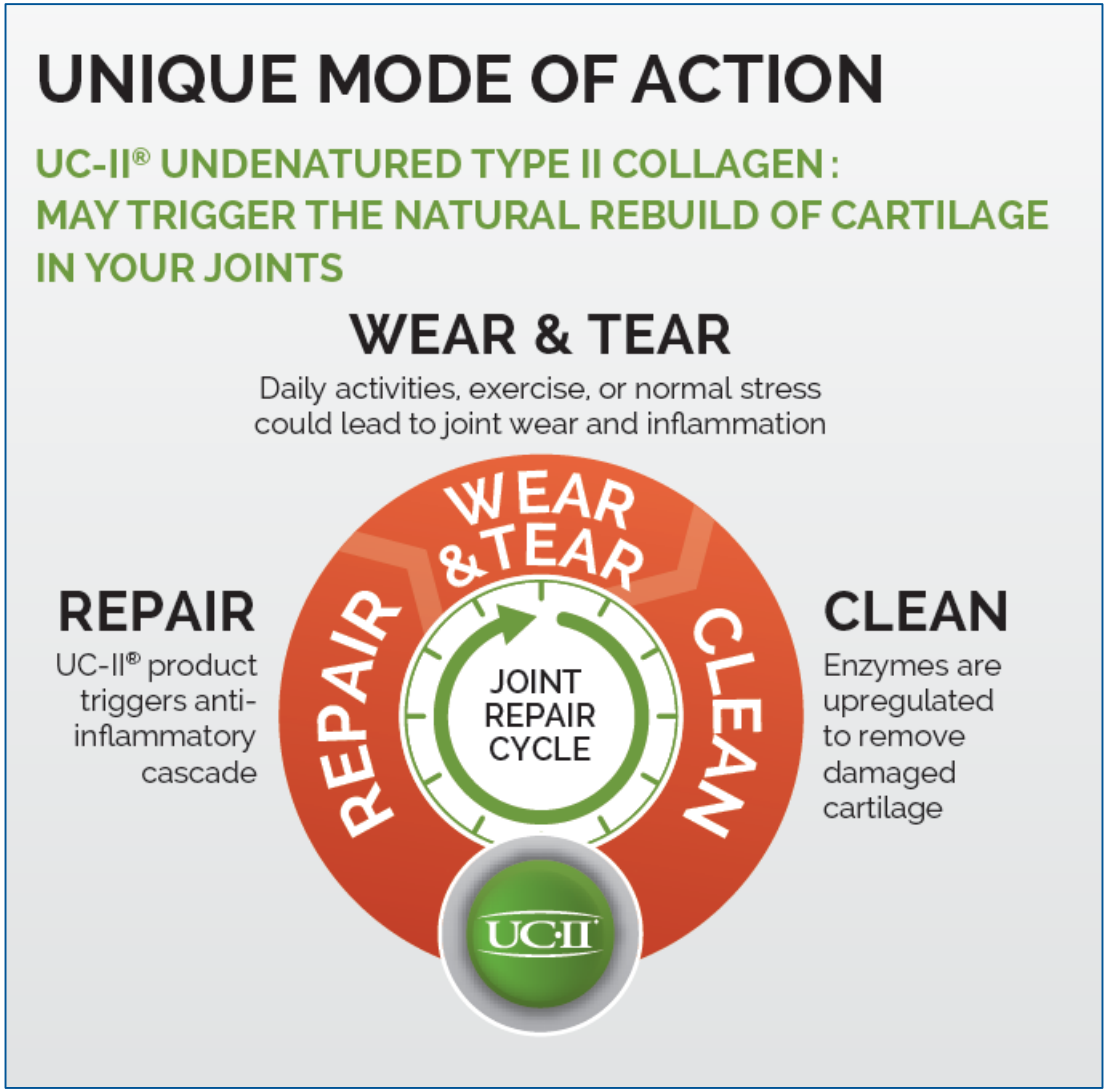
- Daily supplementation with 40 mg of UC-II was well tolerated
- Improved knee joint extension in healthy subjects.
- UC-II significantly increased average knee extension compared to placebo
- UC-II appears to be effective in alleviating joint discomfort in healthy subjects
- Potential to lengthen the period of pain free strenuous exertion
- Alleviate the joint pain that occasionally arises from exercise activities.



UCII : Undenatured Type II Collagen, UCII®

J Int Soc Sports Nutr. 2013;10:48.

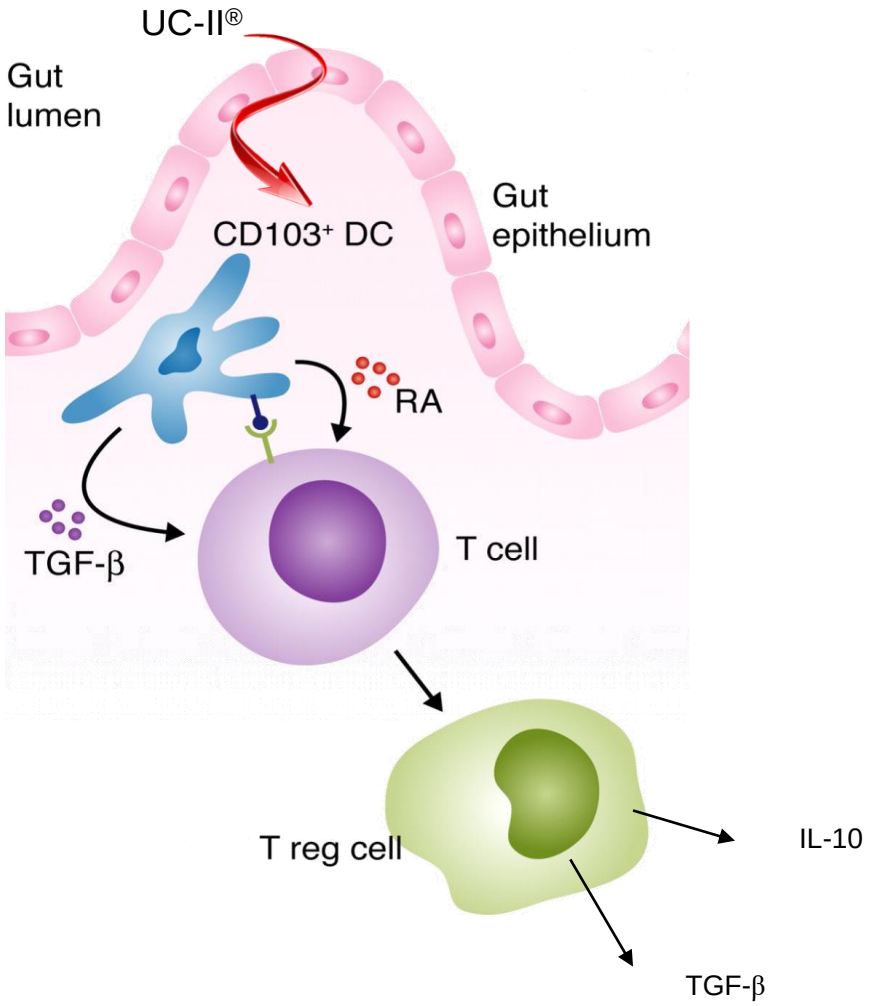
Proposed Mechanism of Action



UCII : Undenatured Type II Collagen, UCII®

Proposed Mechanism of Action

Undenatured type II collagen is adsorbed in the gut and initiates cell-signaling cascades that use the body's natural repair mechanisms.



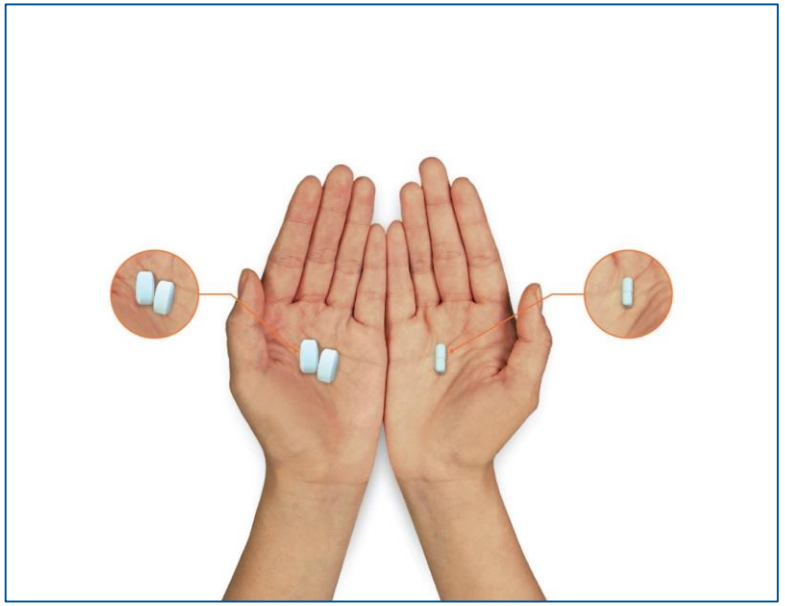
Tregs produce anti-inflammatory cytokines, (IL-10, TGF-β) and may help in repair and cartilage rebuilding

Von Boehmer et al. *Exp Med* 2007;204:1737-1739
Ramage, et al. *Scand J Med Sci Sports*. 2009;19:457-69

UC-II® Undenatured Type II Collagen

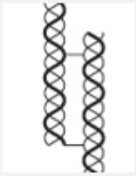
Convenient Dosing that Appeals to Older Adults

- Small, once-a-day dosage, 40 mg/day
- Smaller pills than glucosamine + chondroitin
- Easy to combine with other joint-health ingredients
- Differentiate your product by using unique delivery forms that appeal to older adults



UCII : Undenatured Type II Collagen, UCII®

The UC-II® Undenatured Type II Collagen Difference

	Collagen		
	Undenatured (Native)	Denatured	
		Gelatin	Collagen hydrolysate (Hydrolyzed collagen)
Preparation method	• No heat • No enzyme • Gentle processing	• Partial hydrolysis (heat) • Harsh processing	• Complete hydrolysis (heat + enzyme) • Harsher processing
Triple helical structure	• Retained	• Disrupted	• Disrupted
Structural representation			
Product form	• Intact polypeptides • Active epitopes	• Mixture of peptides and polypeptides • No active epitopes	• Amino acids & small peptides • No active epitopes
Examples	• UC-II®	• Gelita • Jello	• Biocell • Kollagen xs • Peptan

Safety of UCII

International Journal of Medical Sciences
2009; 6(6):312-321

Research Paper

Safety and efficacy of undenatured type II collagen in the treatment of osteoarthritis of the knee: a clinical trial

- LD50 : UC-II, at the limit dose of level of 5000 mg/kg body weight, did not cause any mortality and did not demonstrate any signs of gross toxicity, adverse pharmacologic effects, or abnormal behavior in the treated female rats.
- No mutagenicity either with or without metabolic activation
- No-observed-adverse-effect level (NOAEL) for UC-II was 400 mg/kg/day following daily oral gavage to male and female Sprague-Dawley rats for at least 90 days.

UCII : Undenatured Type II Collagen, UCII®

Regulatory Status

- Food and Drug Administration (FDA)
  - UCII is NDI notified to FDA
- Authorized for sale by Health Canada
- UCII is self affirmed GRAS, reviewed by independent toxicology expert panel
- UCII an approved ingredient for dietary supplements in many countries around the globe

UCII : Undenatured Type II Collagen, UCII®

Provide consumers with a differentiated joint health product UCII® by combining science with small dosage form.

- Maintain flexibility and mobility of joints
- Science Backed
- Small, and easy to take once-daily 40mg dose
- **35% more effective than Glucosamine + Chondroitin**
- Manufactured in USA under GMP
- FDA notified NDI
- GRAS Self Affirmation

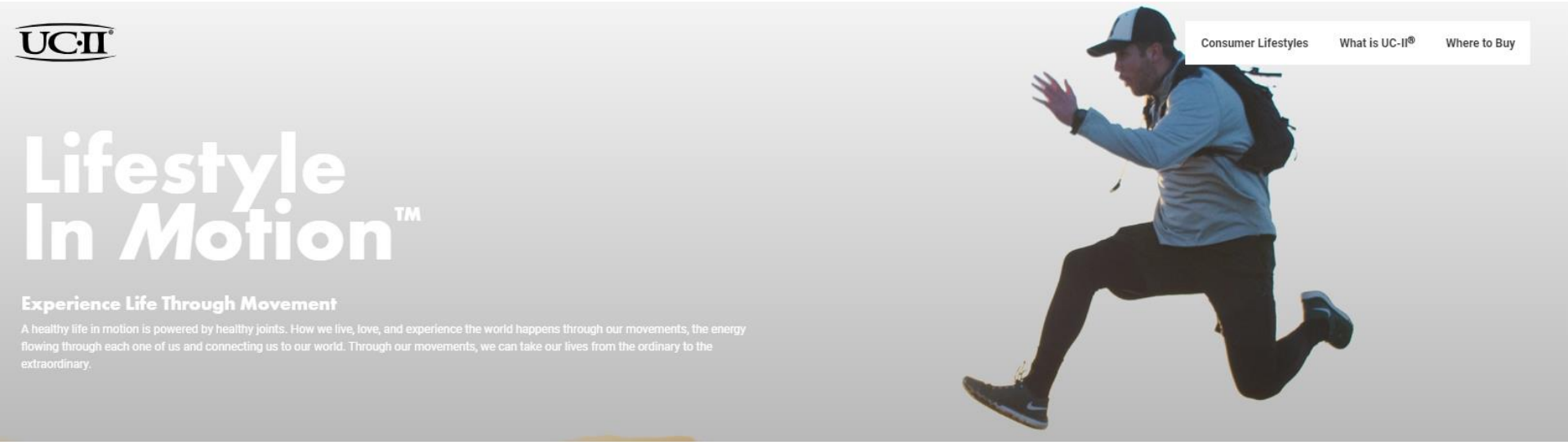
K. Kuhn, 1987, in R. Mayne and R. Burgeson, eds., Structure and Function of Collagen Types, Academic Press, p. 2
Vander Rest M et al. FASEB J., 1991, 5:2814.

Finished Dosage Forms

- UC-II is able to be formulated on it's own or in combination with other ingredients
- Can be utilized in Licap® liquid capsule format, or multiple other dosage form solutions to maximize bioavailability and efficacy

Consumers & Joint Support

- Consumers are looking to physicians to lead them towards better joint health
- All generations are looking for healthy, and natural options to manage their conditions
- Joint discomfort is one of the most concerning health issues for consumers
- Undenatured type II collagen (UC-II®) provides consumer with more benefits than Glucosamine & Chondroitin, including improved efficacy and easier dosing strategies
- Speak to those around you today about their options for supporting their joint health



Corporate

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